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DESIGN AND SIMULATION OF A BRAINWAVE CONTROLLED NEUROPROSTHESIS

by

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Design and Simulation of a Brainwave Controlled Neuroprosthesis

Thesis directed by Professor Carlos A. Paz de Araujo

Every day, an important amount of people have their bodily functions diminished. Spinal cord, nerves, muscles, or any of the five senses function improperly or stop working due to accidents, diseases, or injuries. This is a desperate situation for a patient. He wants to get a sip of his soda but he cannot; human research exists for this, to try to give a solution to problems.

To restore the lost function of injured patients and give them a better life when life is already difficult, that is the objective of neural prostheses, such as a robotic arm. Building a neural prosthesis needs progress on several disciplines like neuroscience, medicine, engineering, biology, and anatomy. Despite being a challenge and knowing it is really difficult, this thesis first reviews what is behind the development and simulation of a brain-controlled prosthetic arm, and then presents a design solution.

We start with a survey of neuromorphic and neural models, and a study of the state of the art in the field of neuroprosthetics. Then, we explain the muscle movement by describing the connection from the brain to the nervous system, and to the muscle. At the muscle we describe this process through electromyography. After that, we translate it to a practical example of a basic design of an arm prosthesis and an EMG simulator, and emphasize on the considerations to be taken into account in a real case scenario. Finally, we show a simple example of how a robotic arm could be controlled with brainwaves, and talk about the future of brain-controlled arm prostheses.

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CHAPTER 1

Introduction

In this thesis, we study the scope of designing a brainwave-controlled neuroprosthesis. We start with a review of three areas that need full consideration in scoping the elements needed to understand the state-of-the-art in this discipline. These areas are covered in Chapters 2, 3, and 4.

In Chapter 2, we cover neuron models, or more specifically, biological neuron models. The original biological neuron model of Hodgkin and Huxley [1] is shown to be able to be reduced to a nonlinear dynamic system with a complicated phase portrait named the FitzHugh-Nagumo model [2, 3].

Prior work in this field is addressed in Chapter 3 with a survey of the state-of-the-art in neuroprosthetics, to illustrate the breadth of this field and to differentiate our studies from invasive (non-autonomous) motor neuroprostheses. Chapter 3 also covers the signal processing and Brain-Computer Interfaces (BCI) common to commercial prostheses.

This review prepares the reader to comprehend the signals originated in neuron firing. Such signals will be the important inputs - in the form of an input current into banks of neurons (nerves) that form the Peripheral Nervous System - that eventually lead to motoneurons in connection to muscle movement as described in Chapter 4. We use signal acquisition via Electromyography (EMG), which studies the composite signal created by the addition of Motor Unit Action Potentials (MUAPs), for the simulation of brain-to-nerve-to-muscle commands involved in motion.

The central chapters of this work are Chapters 5 and 6. The EMG composition model described in Chapter 4 is used in Chapter 5 for simulation of EMG signals. That is, the signals that normally go into muscular excitation can be modeled by the simulator, and thus become the signal source if the nervous ending of an amputated limb cannot supply such signals. It is this point that provide the main theme of this thesis.

The autonomous prostheses would apply such signals from a simulator onto an artificial limb and empower it to perform the required action. Training such an autonomous artificial limb is shown in Fig. 5.1 in Chapter 5 via a learning program (which can use common artificial neural networks like vector-based machines) in which a person's healthy limb can serve as the baseline. A simulator of EMG signals is fully implemented and a graphical user interface for a possible training and design implementation is shown.

The full methodology for design based on the EMG approach is presented. However, full implementation and realization of a working prototype is curtailed due to equipment limitations and development of a multi-degrees of freedom code to translate brainwaves to generate the complex EMG signal patterns.

In Chapter 6, a 3-degrees of freedom "toy model" is fully designed and demonstrated using a brainwave sensor which sends signals via Bluetooth to a computer which controls a robotic arm built with a LEGO based controller. This simple implementation does not use the EMG simulator. It goes directly to the control of the autonomous artificial "robotic arm" and performs motion with the artificial claws, as well as arm movements. The program shows that a more complicated system in which brainwaves can generate EMG-like signals via a translator code from brainwaves to motor signals is possible and well within the capabilities as demonstrated in Chapter 5.

It is the goal of the thesis to narrow the view of developing an autonomous brainwave controlled artificial limb, to the considerations and approach presented by the contents of its chapters. The realization of the design and further work on many aspects of the problem of autonomous prosthesis are discussed for future work in the concluding chapter.

CHAPTER 2

Neurons and classical neuron models

Neurons are one kind of the trillions of cells we have in the human body. They are nerve cells, which make all of the organs, muscles, and veins work. There are about 10 billion neurons in the human brain, all of them interconnected, forming neural networks. Neurons are specialized in transmitting instructions from our brain through electrical or chemical *synapses*. Electrical synapses use electric signals for the transmission of information, whereas chemical synapses use specialized molecules called *neurotransmitters*, which are released in a resting neuron after an action potential propagating from a firing neuron gets to the synapses.

An *action potential* (or *spike*) is an electric signal generated by a change in voltage in the membrane of a nerve cell. It is the smallest unit of information in our brain. In 1952, Hodgkin and Huxley (HH) based their model of the neuron on these small signals in their research in the field of neuroscience [1]. HH performed an experiment by inserting a thin wire inside a giant squid axon to measure the changes in ion currents and how they would affect the neuron firing. They successfully came up with four different equations and a circuit equivalent model which is still the gold standard today for modeling a neuron. HH's is one of the best models to understand how biologically related neuron components like synapses, dendrites, action potentials and single cell ion currents work.

In this chapter we review existing models of neurons. As neurons form the basis for muscle movement, the understanding of neuron models is the first step that we have to consider.

2.1 Neuronal structure

Neurons come in many different shapes and sizes, and they are the oldest and longest cells in the human body. In this section, we explain the main parts of a typical neuron, which are shown in Figure 2.1:

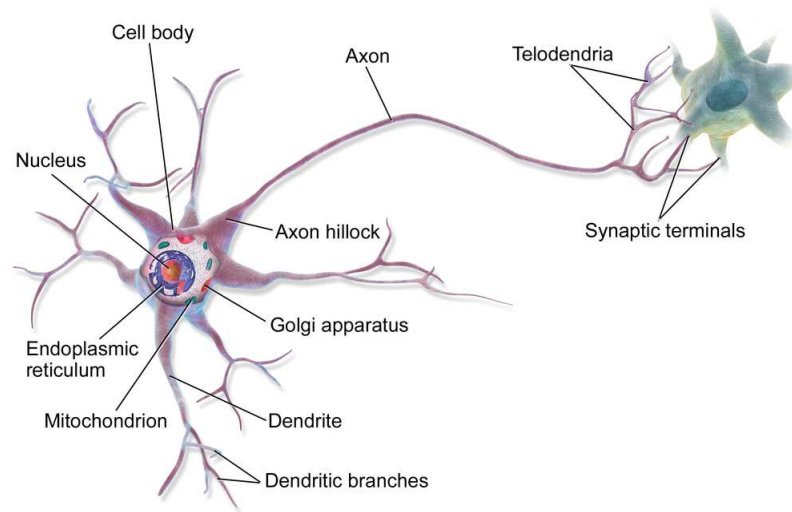


Figure 2.1: A diagram of a typical neuron and its parts [4]

- **Soma**

The *soma* is the cell body of a neuron. As all the other cells, the soma has cytoplasm inside, and a membrane surrounding it. It contains the most important parts of the cell:

- The *nucleus*: contains the genetic material for cell development and neurotransmitter release.
- The *mitochondria*: provides energy to the cell.
- The *ribosomes*: synthesize proteins.
- The *Golgi apparatus*, package proteins and hormones to the vesicles and other organelles.

The soma is the part of the nerve cell where more metabolic activity happens. Collections of somas give the appearance to the grey matter of the brain.

- **Axon**

The *axon* can be seen as a link between neurons. It carries the information away from the soma to other neuron synapses or dendrites. It consists of a long filament projecting from the soma and dividing into several branches at the end called terminal buttons. Its diameter is of about $0.2\text{ }\mu\text{m}$ in humans, although in other species can be really huge - a squid axon can measure up to 1 mm in diameter. The axon's role is to transmit an action potential from one neuron to another. It is covered with a myelin sheath, an insulating layer separated at regular intervals that influences the speed of propagation of action potentials (normally depolarizing them). At any moment, the influence of all neurons that are connected to a given neuron will determine if an action potential will be fired and propagated down the axon.

- **Synapses**

Neurons receive information through synapses (Figure 2.2). Each of the human brains' neurons has around 7,000 synapses that pass electrical or chemical signals to other neurons. Thus, there are two types of synapses:

- *Electrical* synapses, in which the cell membranes are connected by gap junctions that pass electric current causing a firing in the next neuron.
- *Chemical* synapses, that release neurotransmitters, which, at the same time, can initiate a firing in the receiving neuron. Neurotransmitters can be either excitatory or inhibitory, depending if they increase or decrease activity in the target neuron. Some examples of neurotransmitters are serotonin, dopamine, GABA (*gamma*-Aminobutyric acid), and endorphin.

- **Dendrites**

Dendrites are ramifications projecting from a neuron that receives the signals coming from other neurons' synapses and deliver them to the soma. The combination of several dendrites extending from a soma are often referred to as a *dendritic tree*. Dendrites grow in puberty and shorten with senility.

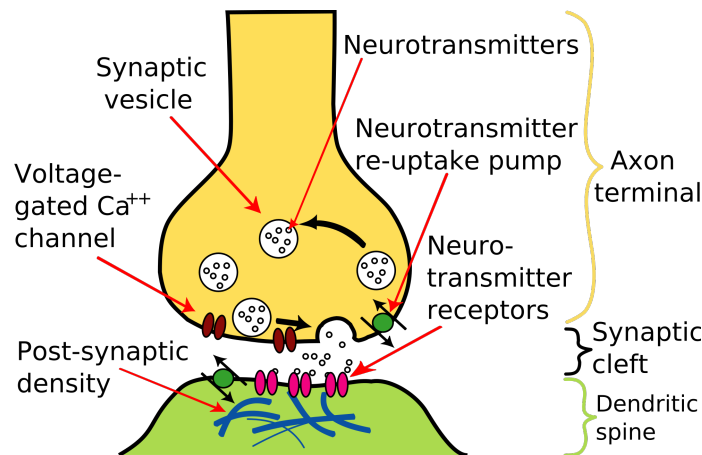


Figure 2.2: A diagram of a synapse. The neurotransmitters are released and received by the dendrite of a resting neuron, possibly causing the firing of an action potential

2.2 The action potential

How do neurons communicate with other neurons? The process depends mainly on the action potential. As said before, an action potential is a short event (measured in milliseconds) that occurs when the membrane voltage of a neuron increases and then decreases rapidly. It is, at the same time, the information carrier between neurons. When a resting neuron emits an action potential, it is usually said that it “fires.” This happens after dendrites have received a combination of electric signals coming from other neurons’ electrical synapses or neurotransmitters released from a chemical synapses, increasing the resting potential. If the increase is large enough (typically over -55mV , called *threshold*) a neuron will fire an action potential.

All action potentials have the same amplitude. The shape of an action potential is explained in Figure 2.3:

1. When the depolarizing current hits the threshold, the sodium voltage channels open and the sodium ions rush into the neuron, causing Phase 1 in the image.
2. Since sodium has a positive charge, the neuron becomes depolarized until it reaches the sodium Nernst potential (explained in section 2.3.1) and the sodium channels close (Phase 2, upstroke).

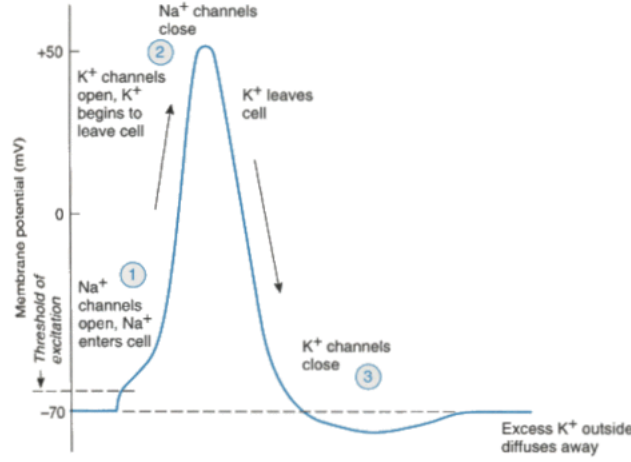


Figure 2.3: A diagram of an action potential

3. The potassium channels open and the potassium ions leave the cell hyperpolarizing it, thus, causing the action potential to go under the resting voltage of -70mV (Phase 3).
4. The refractory period represents the time it takes for the potassium channels to close, and thus for the membrane to go back to the resting potential.

2.3 Classical neuron models

2.3.1 The resting potential, the Nernst equation and the Goldman-Hodgkin-Katz equation

To understand the HH models we have to go back to the basics of the mechanisms of a typical cell [5].

All cells have a potential difference between their inside and outside, called *the membrane potential*, which is defined as

$$V_M = V_{\text{in}} - V_{\text{out}}, \quad (2.1)$$

where V_{in} is the potential on the inside of the cell and V_{out} is the potential on the outside. The membrane potential when the cell is at rest is called the *resting potential* (-70mV for

a typical neuron). When a membrane potential is close to zero, we say it is *depolarized*. On the other hand, if it is negative, it is *hyperpolarized*.

At rest, there are relatively more ions of Na^+ and Cl^- outside the neuron and a large concentration of K^+ ions on the inside. Essentially these three are the main ions we can find in a cell. Through the *voltage-gated* channels, Na^+ and Cl^- ions travel to the inside, and K^+ ions move to the outside. This traveling leaves negative charge on the inside of the cell, which blocks more flow of K^+ until an equilibrium is reached, which we call *Nernst potential* and is expressed in terms of internal and external ionic concentration, the Boltzmann constant k , the temperature in kelvin T , and the charge of an electron q as

$$V_K = -\frac{kT}{q} \ln \frac{[\text{K}^+]_{\text{in}}}{[\text{K}^+]_{\text{out}}}. \quad (2.2)$$

This equation works also for Na^+ and Cl^- . Following Fick's law of diffusion and Ohm's law, the total current flux across a membrane is

$$J_{\text{drift}} = -(\pm zq)\mu[C] \frac{\partial V}{\partial x} \quad (2.3)$$

$$J_{\text{diffusion}} = -D \frac{\partial [C]}{\partial x} \quad (2.4)$$

$$J = J_{\text{drift}} + J_{\text{diffusion}} = -(\pm zq)\mu[C] \frac{\partial V}{\partial x} - D \frac{\partial [C]}{\partial x}, \quad (2.5)$$

where $[C]$ is the concentration of an ion, z is the valence number of the ion, D is the diffusion coefficient, μ the mobility of the ion, and $V(x)$ the potential at a point x across the membrane. D is empirically measured with a typical value $2.5 \times 10^{-6} \text{ cm}^2/\text{s}$. Following Einstein's relation, the relationship between diffusion and mobility is shown below and related to the Faraday number as commonly done in aqueous solutions. Thus,

$$D = \frac{kT}{q} \mu = \frac{RT}{zF} \mu, \quad (2.6)$$

where R is the gas constant and F the Faraday constant. If we convert (2.5) to moles and multiply by z and F we will have electrical current instead of just ion flux. According to Kirchhoff's Current Law, the sum of all diffusion and drift currents have to be zero (Nernst or equilibrium potential is thus achieved). Combining (2.1), (2.2), and (2.6), will give us the *Nernst equation*

$$V_M \equiv V_{\text{in}} - V_{\text{out}} = -\frac{RT}{zF} \ln \frac{[C]_{\text{in}}}{[C]_{\text{out}}}. \quad (2.7)$$

Now, we assume 1-D flow through a cylinder of length L , and that

$$\frac{dV}{dx} = E = -\frac{V}{L}. \quad (2.8)$$

For a constant diffusion coefficient, $\mu = D \frac{zF}{RT}$, the total flux J is

$$J = -D \left(\frac{zF}{RT} [C] \frac{V}{L} + \frac{\partial[C]}{\partial x} \right) \quad (2.9)$$

We are now going to derive the current equation as a function of the cell membrane permeability. Starting with

$$\frac{J}{D} = -\frac{zF}{RT} [C] \frac{V}{L} - \frac{\partial[C]}{\partial x} \quad (2.10)$$

we define $\alpha = \frac{zFV}{RTL}$ to simplify the ordinary differential equation (ODE)

$$\frac{J}{D} = \alpha [C] - \frac{\partial[C]}{\partial x}. \quad (2.11)$$

The ODE can be solved:

$$[C]e^{-\alpha x} = [C]_{in} + \frac{J}{D} \frac{1}{\alpha} (e^{-\alpha x} - 1) \quad (2.12)$$

with boundary conditions at $x = 0$ and $x = L$,

$$[C](0) = [C]_{in} \quad [C](L) = [C]_{out}. \quad (2.13)$$

This gives,

$$J = D\alpha \frac{[C]_{in} - [C]_{out}e^{-\alpha L}}{1 - e^{-\alpha L}} = D \frac{zFV}{RTL} \frac{[C]_{in} - [C]_{out}e^{-\frac{zFv}{RT}}}{1 - e^{-\frac{zFv}{RT}}}. \quad (2.14)$$

The current is given by

$$I = zFJ. \quad (2.15)$$

Now, introduce ξ as a unitless energy ratio,

$$\xi = \frac{zV_M F}{RT} \quad (2.16)$$

and recall the definition of permeability

$$P \equiv \frac{uRT}{lF}, \quad (2.17)$$

where $u = \frac{\mu}{N_A}$, and l is the width of the membrane. Substituting into (2.14), yields the desired result for the current I ,

$$I = PzF\xi \left(\frac{[C]_{\text{out}}e^{-\xi} - [C]_{\text{in}}}{e^{-\xi} - 1} \right). \quad (2.18)$$

(2.18) shows the current due to just one ion species, which depends on whether the membrane voltage is above or below the Nernst potential. If there are three ionic species, K^+ , Na^+ , and Cl^- , the total current will be the sum of the corresponding currents of each species. So at equilibrium ($I = 0$), we have the *Goldman-Hodgkin-Katz (GHK)* equation, for a membrane potential V_M :

$$V_M = \frac{RT}{F} \ln \frac{P_K[K^+]_{\text{out}} + P_{Na}[Na^+]_{\text{out}} + P_{Cl}[Cl^-]_{\text{out}}}{P_K[K^+]_{\text{in}} + P_{Na}[Na^+]_{\text{in}} + P_{Cl}[Cl^-]_{\text{in}}}. \quad (2.19)$$

2.3.2 The Hodgkin-Huxley model

A simple way to understand how a neuron generates action potentials is to model them as electrical circuits.

The equivalent circuit of a membrane permeable only to potassium is shown in Fig 2.4. The relationship between the charge and the voltage of the membrane is shown by

$$q = C_M V_M, \quad (2.20)$$

where C_M is the total capacitance in the membrane. Normalizing the capacitance by area, we define c_M , which has a value very close to $1 \mu\text{F}/\text{cm}^2$. Thus, the current through the capacitance is given by

$$i_{\text{cap}} = c_M \frac{dV_M}{dt}. \quad (2.21)$$

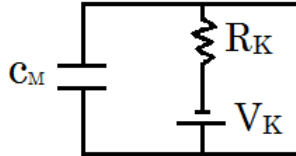


Figure 2.4: A circuit representing a cell membrane formed by an insulating lipid bilayer and a K^+ channel, which allows current to flow.

In Figure 2.4, a resistor in series with a voltage source that represents the potassium channel is shown. By Ohm's Law, the potassium current through the channel is

$$I_K = g_K(V_M - V_K), \quad (2.22)$$

where g_K is the conductance of the potassium channel and V_K is the voltage coming from the source, given by (2.7). Since Kirchhoff's Current Law states that the total current going into the cell must sum zero, then

$$i_{\text{cap}} + I_K = c_M \frac{dV_M}{dt} + g_K(V_M - V_K) = 0. \quad (2.23)$$

Assuming the voltage is the same across the entire membrane, the membrane potential satisfies

$$c_M \frac{dV}{dt} = -g_{\text{Na}}(V - V_{\text{Na}}) - g_K(V - V_K) - g_L(V - V_L). \quad (2.24)$$

Here, g_{Na} and g_K represent the sodium and potassium channels' conductance, and can change with time, whilst g_L is constant. $I_L \equiv g_L(V - V_L)$ represents the passive flow of ions through nongated channels, and is called the *leakage current*.

In 1952, Alan Lloyd Hodgkin and Andrew Huxley [1] demonstrated this by using a giant squid axon, and modeled the neuron as the circuit equivalent shown in Figure 2.5.

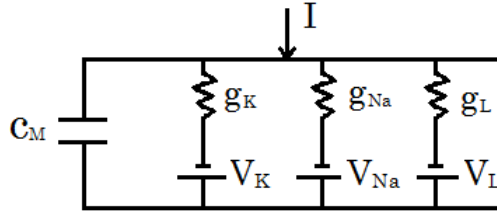


Figure 2.5: Equivalent circuit underlying the Hodgkin–Huxley equations

To do so, they used two techniques:

- The *voltage-clamp*, by which they held the membrane at a certain voltage level, making the capacitive current equal to zero

- The *space-clamp*, by which they managed to insert a conductive wire inside the axon (squid axons can be 100-1000 times larger than a mammalian axon) and short-circuited the axoplasm making it isopotential over its length.

Then, they assumed the squid axon could be modeled as a finite cylinder of radius a , which adds a voltage-in-a-cable term to (2.24), and goes to zero after space-clamping:

$$c_M \frac{dV}{dt} = \frac{a}{2r_L} \frac{\partial^2 V}{\partial x^2} - g_{Na}(V - V_{Na}) - g_K(V - V_K) - g_L(V - V_L) + I_{app}, \quad (2.25)$$

where r_L is the specific intracellular resistivity.

After that, they proceeded to calculate the value of the conductances. First, as voltage clamping was done, they set the membrane to a constant potential. Potassium and sodium do not influence when the membrane is at rest, and thus the total current was given only by the leakage current. By knowing V (the voltage at which the membrane was set), V_L , and the observed current I_L , they could solve for g_L from $I_L \equiv g_L(V - V_L)$.

Second, they replaced the sodium ions in the external solution by an inactive cation, removing the sodium current. Once the sodium current was gone, the voltage clamp was used to calculate I_K by subtracting the leakage current from the total current. Once knowing I_K and I_L , I_{Na} was computed subtracting I_K and I_L from the total current. Then, the conductances for sodium and potassium were calculated using Ohm's law:

$$g_K = \frac{I_K}{V_M - V_K} \quad \text{and} \quad g_{Na} = \frac{I_{Na}}{V_M - V_{Na}}. \quad (2.26)$$

After trying several values for the voltage clamp, HH proposed that

$$g_K = \bar{g}_K n^4 \quad \text{and} \quad g_{Na} = \bar{g}_{Na} m^3 h, \quad (2.27)$$

where $\bar{g}_K$ and $\bar{g}_{Na}$ are maximum conductances and n , m , and h are gating variables that take values between 0 and 1. Here, n^4 represents the probability that a K^+ channel is open. The probability that the sodium activation gate is open is m^3 and the probability that the sodium inactivation gate is open is h . Thus, the Hodgkin and Huxley model is described via four equations: the current equation

$$c_M \frac{dV}{dt} = -\bar{g}_K n^4 (V - V_{Na}) - \bar{g}_{Na} m^3 h (V - V_K) - g_L (V - V_L) + I, \quad (2.28)$$

and four rate equations that determine the rate of the gating reactions to a change in effective densities of ions (n , m , and h) to the time constants of their decay to levels at the resting potential. Thus,

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n = (n_\infty(V) - n)/\tau_n(V) \quad (2.29)$$

$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m = (m_\infty(V) - m)/\tau_m(V) \quad (2.30)$$

$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h = (h_\infty(V) - h)/\tau_h(V). \quad (2.31)$$

If $X = n$, m , or h , then

$$X_\infty(V) = \frac{\alpha_X(V)}{\alpha_X(V) + \beta_X(V)} \quad \text{and} \quad \tau_X(V) = \frac{1}{\alpha_X(V) + \beta_X(V)}, \quad (2.32)$$

where $X_\infty(V)$ corresponds to a normalized ratio of densities.

Hodgkin and Huxley chose the following parameters and gating functions: $\bar{g}_{\text{Na}} = 120 \text{ mS/cm}^3$, $\bar{g}_{\text{K}} = 36 \text{ mS/cm}^3$, $\bar{g}_{\text{L}} = 0.3 \text{ mS/cm}^3$, $V_{\text{Na}} = 50 \text{ mV}$, $V_{\text{K}} = -77 \text{ mV}$, $V_{\text{L}} = -54.4 \text{ mV}$. Using these values and $V_{\text{rest}} = -65 \text{ mV}$, a response for the first equation of the HH model was simulated in this thesis using MATLAB, as shown in Figure 2.6. If the current is large enough for a long time, the model shows a periodic action potential.

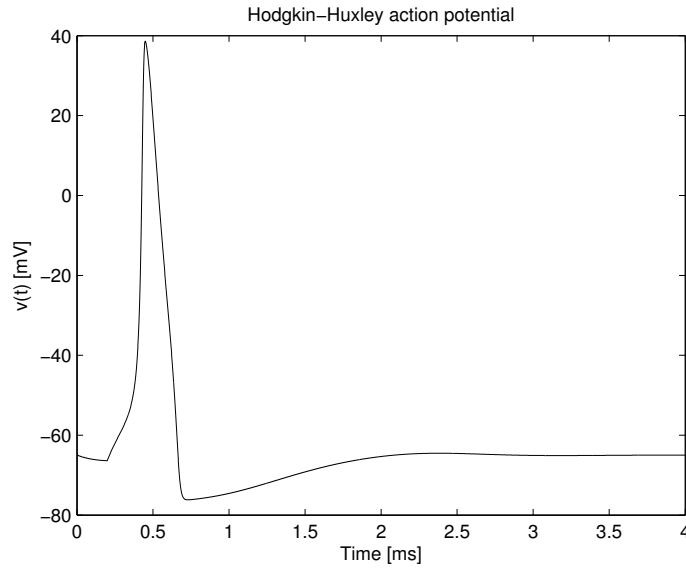


Figure 2.6: Action potential generated by the Hodgkin and Huxley equations, created with MATLAB

In Figure 2.7, the activation curves n , m , and h are plotted. It is shown that, n and m become activated when the membrane is depolarized. Na^+ channels are inactive when the membrane is depolarized. It is also important to note that m decays faster than n and h , so $\tau_m(V)$ is considerably smaller than $\tau_n(V)$ or $\tau_h(V)$. Thus, Na^+ channels activate much faster than they become inactive or K^+ channels open. The action potential described by HH, and as shown in Figure 2.6 and 2.7, is a classical description of a neuron firing due to just the action of K^+ and Na^+ .

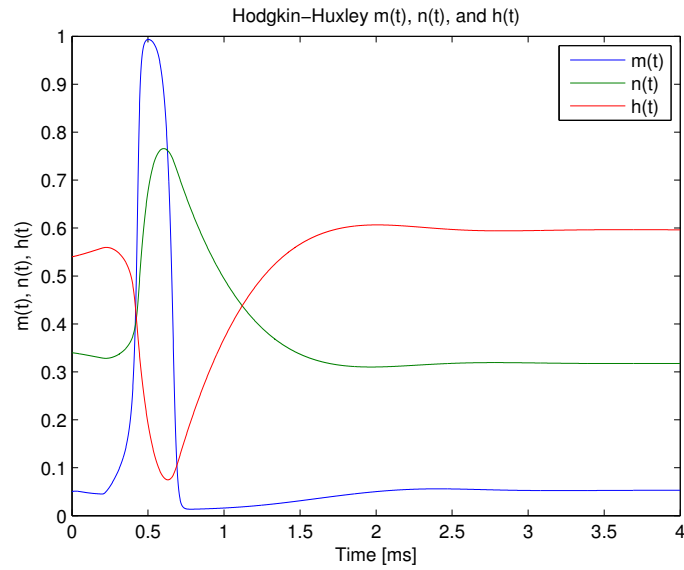


Figure 2.7: Hodgkin-Huxley dynamic functions simulated with MATLAB

2.3.3 The Morris-Lecar Model

Dynamical systems theory provides a powerful tool for analyzing nonlinear systems of differential equations, including those that arise in neuroscience. This theory allows us to interpret solutions geometrically as curves in a phase space. By studying the geometric structure of phase space, we are often able to classify the types of solutions.

A simplified model representing the neuron firing of action potentials is the Morris-Lecar model. It was derived in 1981 by Cathy Morris and Harold Lecar [6] and it is one of the most popular conductance-based models for computational neuroscientists since it works on two variables unlike the Hodgkin and Huxley model, which works with four. Although

this model is considerably simpler than the Hodgkin–Huxley equations, it still exhibits many important features of neuronal activity. For example, the Morris–Lecar model generates the full response of action potentials, contains a threshold for firing, and displays sustained oscillations at elevated levels of an applied current.

Morris and Lecar used a voltage-sensitive Ca^{2+} conductance for excitation and a voltage-dependent K^+ conductance for recovery. The Ca^{2+} “gating” is a very important addition which leads to the inclusion of neurotransmitter release. The model equations are

$$c_M \frac{dV}{dt} = I - g_L(V - V_L) - g_{\text{Ca}} m_\infty(V)(V - V_{\text{Ca}}) - g_K n(V - V_K) \quad (2.33)$$

$$\frac{dn}{dt} = \phi(n_\infty(V) - n)/\tau_n(V) \quad (2.34)$$

where

$$m_\infty(V) = \frac{1}{2}[1 + \tanh((V - V_1)/V_2)] \quad (2.35)$$

$$\tau_n(V) = 1/\cosh((V - V_3)/(2V_4)) \quad (2.36)$$

$$n_\infty(V) = \frac{1}{2}[1 + \tanh((V - V_3)/V_4)] \quad (2.37)$$

and I , V , C_M , g_L , g_{Ca} , g_K , V_L , V_{Ca} , and V_K , are the same as in section 2.3.2, with calcium instead of sodium. ϕ is the reference frequency, and V_1 , V_2 , V_3 , and V_4 , are the tuning bifurcation parameters.

These equations describe the three ionic currents in the HH model by just using two dynamical variables (V and n). The sodium inactivation process is omitted with the approximation that the recovery variable responds more rapidly than the membrane capacitive time constant.

In Figure 2.8a, a solution of the Morris-Lecar equation is shown. Depending on I , as long as the membrane voltage value is over a threshold, the neuron will fire an action potential. In Figure 2.8b, for a large I (i.e. $I = 100$), a periodic action potential is generated.

2.3.4 The Phase Plane

Now that we have a model using two dynamic variables and thus suitable for phase space analysis, it is convenient to write (2.33) as

$$\frac{dV}{dt} = f(V, n) \quad (2.38)$$

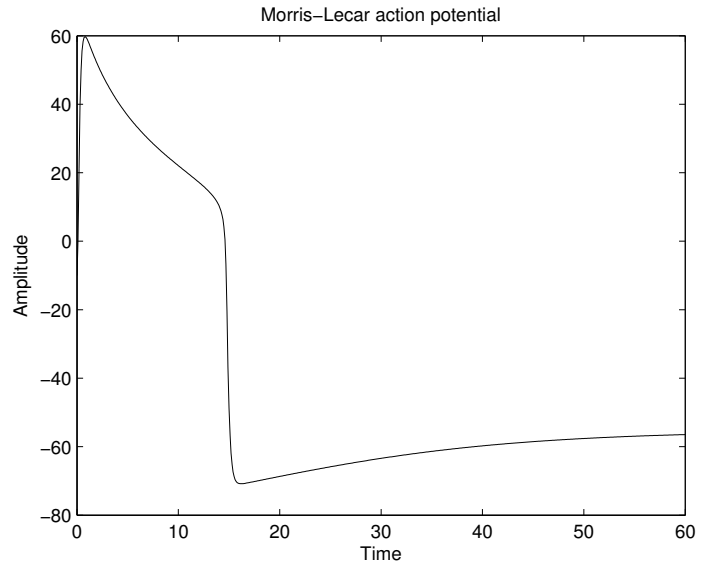
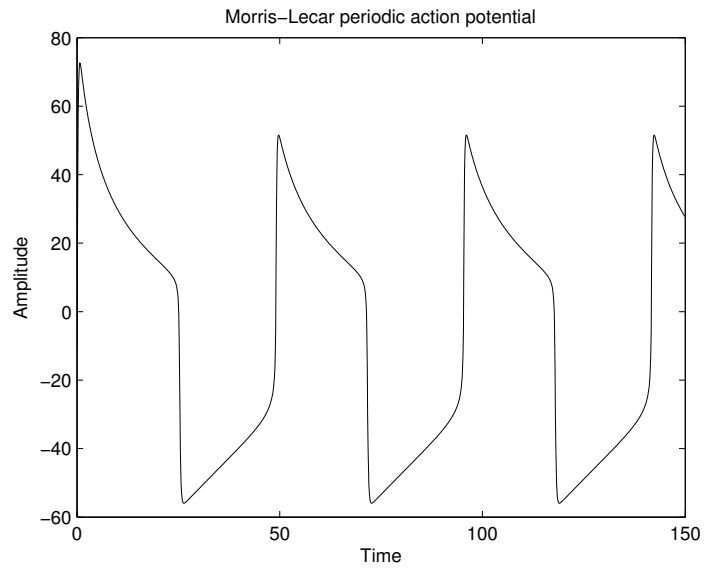
(a) $I = 10$ (b) $I = 100$

Figure 2.8: Solutions of the Morris-Lecar equations (action potentials), created with MATLAB

$$\frac{dn}{dt} = g(V, n), \quad (2.39)$$

where (V, n) is usually referred to as the phase plane. If $(V(t), n(t))$ is a solution of (2.38) and (2.39), then at each time t_0 , $(V(t_0), n(t_0))$ defines a point in the phase plane. The point changes with time, so the entire solution $(V(t), n(t))$ traces out the state (voltage) evolution due to n (effective density) in the phase plane. The orbits of a phase-plane are shown as the response of the FitzHugh-Nagumo model in Figure 2.10 in section 2.3.6.

Two important types of curves are *fixed points* and *closed orbits*. At a fixed point, $f(V_0, n_0) = g(V_0, n_0) = 0$; this corresponds to a constant solution. Closed orbits correspond to periodic solutions. A useful way to understand how trajectories behave in the phase plane is to consider the *nullclines* (where V and n are in dynamic equilibrium). The V -nullcline is the curve defined by $V' = f(V, n) = 0$, and the n -nullcline is where $n' = g(V, n) = 0$. Fixed points are where the two nullclines intersect. The nullclines divide the phase plane into separate regions.

2.3.5 Reduction of the Hodgkin–Huxley Model to a Two-Variable Model

We shall describe two ways in which dynamical systems methods can be used to formally reduce the four-dimensional HH model to a two-dimensional system of equations.

The first observation is that $\tau_m(V)$, the voltage-dependent time constant for the gating variable m , is much smaller than both τ_h and τ_n . Because τ_m is small, $m(V(t))$ is very close to $m_\infty(V)$. If we replace m by $m_\infty(V)$ in the voltage equation, then this reduces the HH model by one equation. The second observation is that $(n(t), h(t))$ lies nearly along a line $n = b - rh$, where b and r are constants.

Each voltage dependent gate $x(t)$ satisfies an equation of the form

$$x' = (x_\infty(V) - x)/\tau_x(V), \quad (2.40)$$

where x' is the derivative of $x(t)$, $\frac{dx}{dt}$.

With the introduction of a new variable V_x for each gate, where $x(t) = x_\infty(V_x(t))$, an equivalent dynamical system can be obtained, every variable having voltage dimensions. The equivalent potentials satisfy

$$\frac{dV_x}{dt} = \frac{x_\infty(V) - x_\infty(V_x)}{\tau_x(V)x'_\infty(V_x)}, \quad (2.41)$$

where $x'_\infty(V_x)$ is the derivative of x_∞ with respect to V .

A reduced model is created by setting $V_m = V$ and $V_n = V_h$. The system for h has the following form (analogous form for n)

$$c_M \frac{dV}{dt} = I_{\text{app}} - \bar{g}_{\text{Na}} m_\infty^3(V) h_\infty(V_h) (V - V_{\text{Na}}) - \bar{g}_{\text{K}} n_\infty^4(V_h) (V - V_{\text{K}}) - \bar{g}_{\text{L}} (V - V_{\text{L}}) \quad (2.42)$$

$$\frac{dV_h}{dt} = \frac{h_\infty(V) - h_\infty(V_h)}{\tau_h(V)h'_\infty(V_h)}. \quad (2.43)$$

The reduced model continues oscillating at a large applied current, in the same way as in the HH model.

2.3.6 The FitzHugh–Nagumo model

In 1961, FitzHugh [2], and Nagumo in 1962 [3] reduced the HH model from four differential equations to two with approximations that did not change the dynamics of the system, making the model easier to understand and compute. Their motivation was to separate the excitation dynamics from the electrochemical properties of K^+ and Na^+ ions flow.

The model captures the essence of the cubic nature of the V -nullcline and has many of the properties of the more complicated models that we have already discussed. The V -nullcline has a cubic shape, whereas the recovery nullcline is a one-to-one increasing function of voltage. The equations have the form

$$\frac{dV}{dt} = V(V - a)(1 - V) - w + I \quad (2.44)$$

$$\frac{dw}{dt} = \epsilon(V - \gamma w), \quad (2.45)$$

where $0 < a < 1$, $\epsilon > 0$, and $\gamma \geq 0$. This behavior is typical for spike generations (a short, nonlinear rise of the membrane voltage V , reduced over time by a slower, linear recovery variable w) in a neuron after stimulation by an external input current (Figure 2.9).

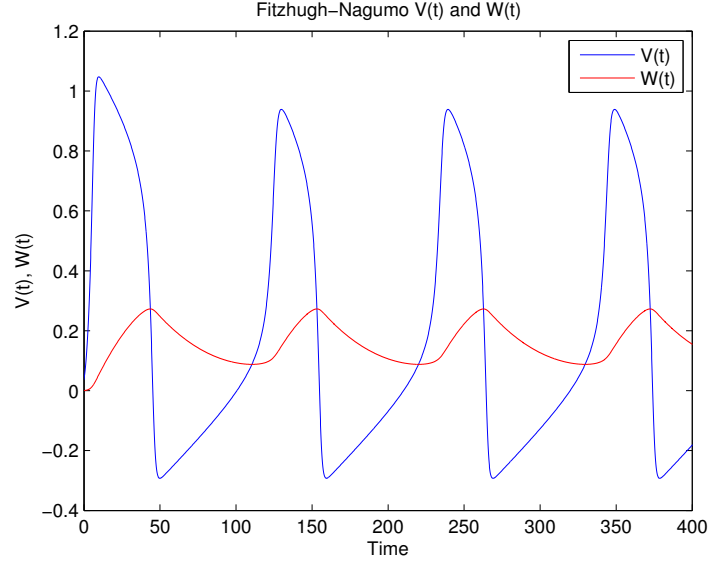


Figure 2.9: FitzHugh-Nagumo model responses, with $a = 0.1$, $\epsilon = 0.01$, $\gamma = 1$, $I = 0.1$

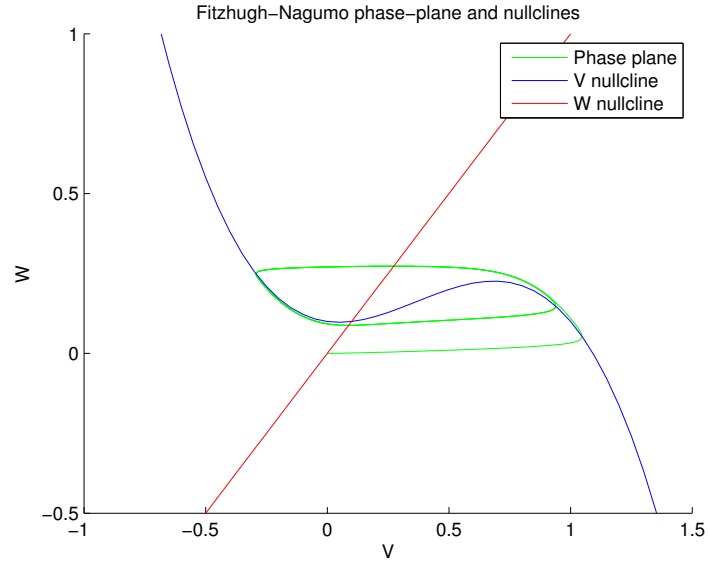


Figure 2.10: The FitzHugh-Nagumo phase plane, with $a = 0.1$, $\epsilon = 0.01$, $\gamma = 1$, $I = 0.1$

One of the possible paths (depending on model parameters and initial conditions) is shown in Figure 2.10: a V -nullcline ($\frac{dV}{dt} = 0$) in blue, a w -nullcline ($\frac{dw}{dt} = 0$) in red, and the trajectory of the phase plane in green. The cross between the two nullclines is an equilibrium point, and the fact of having an external current I shifts the equilibrium point along the

cubic nullcline, displaying different phase-plane paths representing an action potential if I exceeds a threshold value before V and w return to their resting states.

The actual model is based on a modification of the well known van der Pol oscillator equation

$$C \frac{dV}{dt} + F(V) + J = 0 \quad (2.46)$$

$$L \frac{dJ}{dt} = V. \quad (2.47)$$

The van der Pol equation comes from an electrical circuit with a linear capacitor, linear inductor, and nonlinear resistor in parallel. C is the capacitance, L the inductance, $F(V)$ a nonlinear current depending on the voltage, V , across the capacitor, and J the current through the inductor. By adding a driving current and the additional $-\gamma w$, FitzHugh created a model for the action potential.

The FHN equations have been used to model many physiological systems from nerve to heart to muscle and is a favorite model for the study of excitability. In most applications, ϵ is small, so the recovery variable is much slower than the voltage. When $I = 0$ and γ is small enough, there is a unique fixed point at the origin. As I increases, this fixed point becomes unstable through a Hopf bifurcation and a limit cycle emerges.

2.3.7 Concluding remarks

This chapter highlighted the main models of neuronal activity as it refers to action potentials. From the electrochemical HH model, to reductions in dimensionality culminating with the FH model, the emphasis was on neuron firing. The dynamic system reduction is useful in understanding the time response of neuroprostheses, as they react to signals from the brain to the local neuron population that will excite an organ or the muscles. In Chapter 5, we will discuss the electrical activity of muscles excited by neurons.

CHAPTER 3

Neuroprosthetics: a review

Neuroprosthetics or *neural prosthetics*, is a term that refers to the field inside neuroscience that studies neural prostheses. Neural prostheses are instruments that connect with the nervous system and replace or support functions lost by disease or injury. These devices transform the electricity generated by neurons into signals which are transformed and decoded to control devices such as cochlear implants, prosthetic hands or epilepsy preventors.

Neural prosthetics systems rely on the detection and processing of brain activity. Electric signals coming from neurons are normally acquired using recording electrodes (placed on the skull, on the surface of the brain, or within the brain tissue itself) and then decoded into a certain machine control language through a *Brain-Computer Interface* (BCI). This kind of interface is able to extract reliable data from neural action potentials or firing spikes that provide detailed information about the cognitive intentions of the subjects. The spikes are then converted to a suitable output to be used by the final applications.

Neural prostheses are continuously used in animal experimentation before being used in humans, in order to have a better understanding of brain functioning and to start developing early lab prototypes. They are also thought to be minimally invasive (implants have become smaller and brain-device communications have become wireless), relatively inexpensive and easy to manufacture. This type of technology gives hope, for instance, to blind, deaf, or mute people, since they could use neuroprosthetics to interact and communicate with their environments. A person with an injury to the spinal cord could move his/her legs with the help of neuroprosthetics: the device would stimulate the leg muscles after getting the instruction from the brain.

In this chapter we perform a short review of neuroprosthetics, their history, the technology used, and their types. Emphasis is also given to signal acquisition, signal processing

and electroding, as they are central to the neuroprostheses design kit. We also discuss brain-waves as a convoluted action from many neurons, since their use in autonomous prostheses is the application of this thesis.

3.1 History

The study of neuroprosthetics and BCIs started long before it became an academic field. In 1962, Hubel and Wiesel recorded signals from the visual cortex of cats and found that particular neurons only fired when the stimulus moved in a certain direction [7]. In other words, some neurons would fire when a pattern was shown, while others responded best to a different pattern. This experiment was part of a research that continued through the years and led them to win the Nobel Prize in Medicine in 1981.

Grey Walter used the *electroencephalogram* (EEG) to control a slide projector in 1964 [8]. Using the same technology and *visual evoked potentials* (VEP) on a patient, in 1973, Jacques Vidal was the first to come up with the idea of the name Brain-Computer Interface, by building a BCI with the purpose of controlling a cursor in a display [9].

The first procedure involving humans using an implantable device and interacting with a computer took place in 1998 by Kennedy and Bakay [10]. They managed to implant an electrode in the cortical area for the first time, and with *Magnetic Resonance Imaging* (MRI) they detected that the patient showed control of her neuron firing activity using cognitive efforts. Serruya et al. [11] and Taylor et al. [12] showed in 2002 that primates could control and move a computer cursor and later a 3-D prosthetic device in real-time by only using neurons (hands-free). In 2006, Hochberg et al. proved that a tetraplegic patient could open and close a prosthetic hand by just thinking of hand movement [13]. The process was made using electrocorticography (ECoG).

This small example of history is intended to show that neuroprosthetics as a research field has become enormous in the last 40 years, involving fields like biomedical, electrical, and manufacturing engineering, computer science, signal processing, neuroscience, and clinical rehabilitation. For decades, researchers have used neuroprosthetics as ways to surpass neural

deficits or disorders due to injury or disease. Nowadays, brain implants are even able to restore some level of function in patients with sensory or motor disabilities.

Probably the most famous neuroprosthetic device in film history shows up at the end of the movie *The Empire Strikes Back*, where Luke Skywalker is trying a new, robotic hand to replace the one cut off by his father's lightsaber.

3.2 BCI

A Brain-Computer Interface (BCI) is a system that restores or improves the central nervous system (CNS, brain and spinal cord) and changes its interactions with the environment. In other words, it converts the outputs of the CNS into artificial signals that can be used on the exterior (neural prosthesis) or on the body itself. Some of the examples of what BCIs are used for are: restoring injuries, speech converters, stimulation of paralyzed muscles or any kinds of nerves, stopping distracting breaks or epilepsy attacks, or control of a robotic arm or hand.

A BCI that does not depend on natural CNS output is called an independent BCI. For example, muscle activity is not needed to generate the crucial brain signals. Independent BCIs are more effective with people with neuromuscular disorders. An hybrid BCI can use two types of brain signals (e.g. EEG and LFP - refer to section 3.3), it can also be a BCI-muscle based output.

As shown in Figure 3.1, a BCI is composed of basically 3 blocks: signal acquisition, signal processing, and command device for BCI applications. They are explained in detail in the next three sections with emphasis on BCI applications' state-of-the-art in Section 3.5.

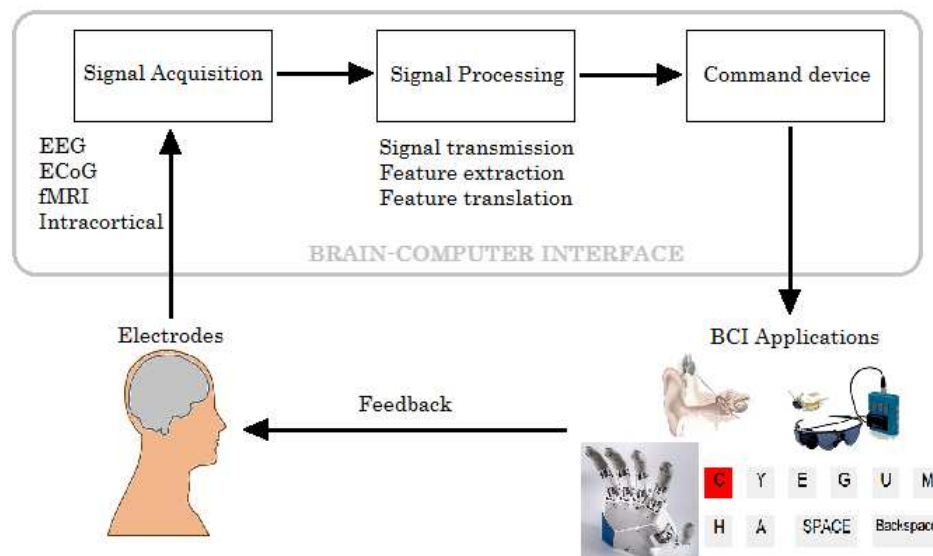


Figure 3.1: A diagram showing the main components of a BCI

3.3 Signal acquisition

Signal acquisition is essential for the development of any neural prosthesis. This block captures signals from the environment using a determined sensor, connecting the biological world with the implanted device. For most of the cases, this sensor is one or a combination of several electrodes (explained in section 3.3.1). It amplifies the signals to help further processing, and filters them to remove noise coming from interference sources. Then the signals are transferred to the next block, signal processing, where they are digitized and sent to a computer. The different methods for signal acquisition are often classified in terms of invasiveness, resolution, and cost.

3.3.1 Electrodes

Electrodes with metal stimulation are sensors being used to restore sensory or motor deficits. They acquire signals from the brain or spinal cord, so they play a very important role in neural prostheses.

The main issues an engineer can encounter when designing an electrode are

- *Size.* The desire is to design a tip area as small as the size of surrounding neurons so stimulation of a specific neuron can be chosen.
- *Tissue damage.* Electrodes can damage brain tissue or cause brain injuries if not designed properly.
- Functional *lifetime* of the device, as well as reliability of the obtained signals.
- *Pulse stimulation.* Stimulation is applied as rectangular current pulses resulting in a null charge balance for the pulse to avoid electrode damage [14] [15]. Stimulating a zone causes a response since the membrane potentials become depolarized. A typical stimulation pulse waveform is shown in Figure 3.2. For charge balance, $I_+ \times t_+ = I_- \times t_-$. The currents are typically between $1 \mu\text{A}$ and $10 \mu\text{A}$, pulses between $50 \mu\text{s}$ and 10 ms (except for $t_d = 0 - 1 \text{ ms}$), and with frequency between 10 and 250 Hz .

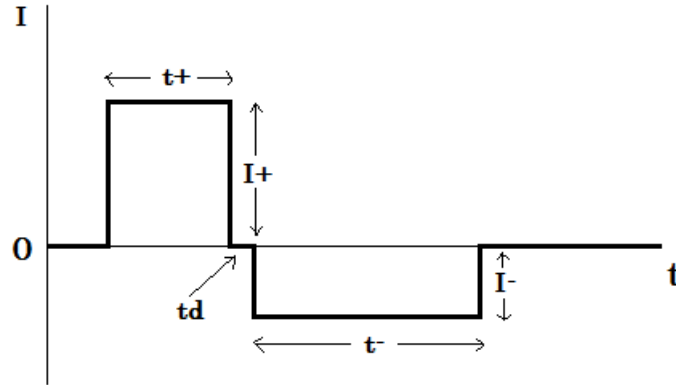


Figure 3.2: A typical stimulation pulse waveform

Single-metal wire electrodes like the ones shown in Figure 3.3a have been the most popular type of electrode used until the last decade. However, more sophisticated prostheses have required a larger number of implanted electrodes, usually grouped together in a matrix or array (Figure 3.3b). Even 3-D electrodes with other design variations have been designed and used in vivo due to their bigger neuron stimulation selection [16] [17] (Figure 3.3c).

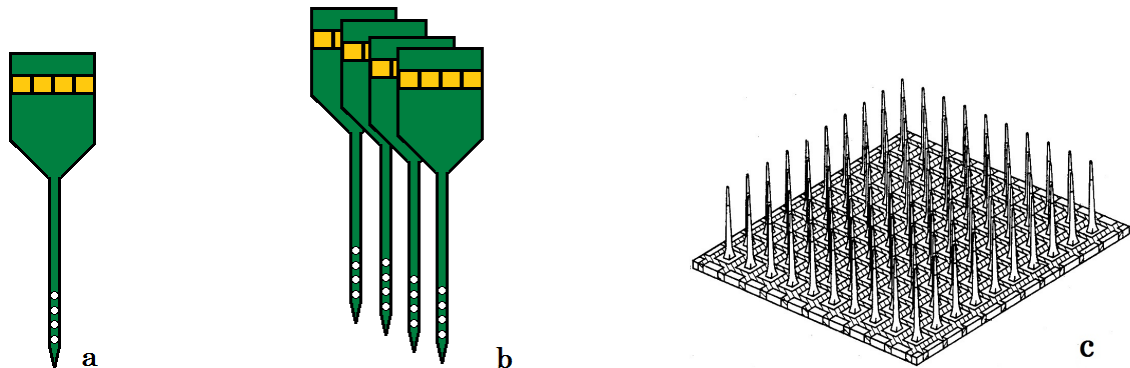


Figure 3.3: . a) A single wire electrode. b) an electrode array. c) a three-dimensional multielectrode array diagram presented by the University of Utah

3.3.1.1 Materials to build electrodes

- *Capacitor* electrodes are interesting since they avoid electrolysis of water, electrode dissolution, or other irreversible electrochemical reactions that might degrade either the electrode or the surrounding tissue. They inject charge entirely by capacitive charging and discharging of the electrode layer.
- *Titanium nitride* (TiN) capacitor electrodes. TiN is a porous metallic conductor deposited as coating.
- *Faradaic* electrodes, based on noble metals, transfer charge by surface reduction and oxidation of a monolayer oxide film. They have been used for studies of intracortical stimulation of the visual cortex.
- *Activated Iridium Oxide Film* (AIROF) is a Faradaic electrode coating based on a three-dimensional film of hydrated iridium oxide. Is capable of injecting charge at levels appropriate for stimulating small populations of cortical neurons using small area electrodes [15].

3.3.2 Electroencephalography (EEG)

Electroencephalography (EEG) is a medical technique that registers the electric signals coming from the brain over a certain period of time. It is the method of signal acquisition

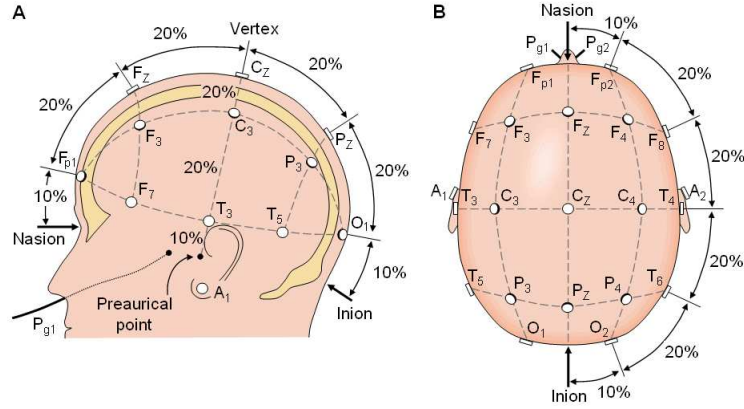


Figure 3.4: The international 10-20 system to place the electrodes to perform an EEG [18]

by far most used. The electrical activity (provoked by ion currents) coming from neurons, is recorded using several electrodes placed on the scalp (many EEG-based BCI systems use an electrode placement strategy based on the International 10/20 system as shown in Figure 3.4), monitoring ranges from 0-300 mV in voltage and 0-50 Hz in frequency [18]. The output obtained by researchers are neural oscillations of several frequencies associated with different states of brain functioning. In Figure 3.5 there are some examples of the different waves that can be obtained with EEG:

- *Alpha*: 8–13 Hz, happen on a rested state.
- *Beta*: 14–25 Hz, occur under patient's tension.
- *Theta*: 4–7 Hz, emitted during emotional stress, disappointment, or frustration.
- *Delta*: < 3.5 Hz, typically happen during deep sleep or in cases of serious organic brain disease.

EEG can be used to distinguish epileptic attacks from other seizures as fainting or migraine, to predict brain death in patients with coma, or to simply diagnose encephalopathy (certain electrical patterns represent certain diseases).

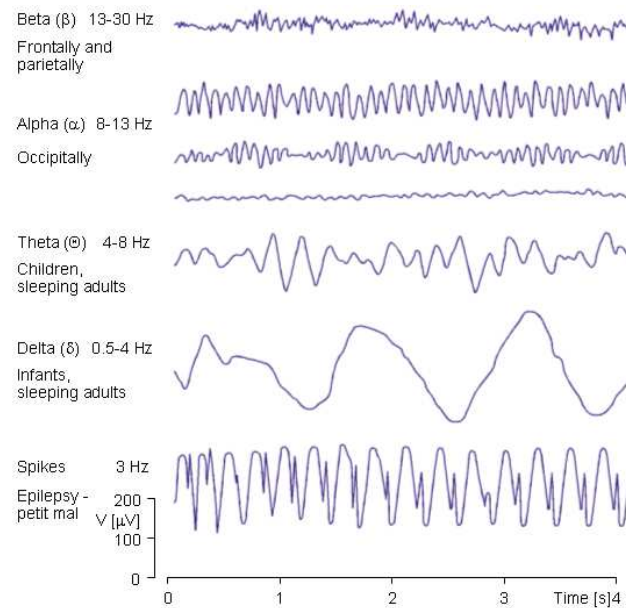


Figure 3.5: Some examples of EEG waves [18]

Advantages

- Portable equipment easy to handle
- Inexpensive and available immediately in high traffic hospitals
- High temporal resolution (milliseconds), sampling rate up to 20,000 Hz
- Noninvasive, silent and tolerant for subject movement

Limitations

- Does not show action potentials directly as an output
- A large amount of neurons firing at the same time is needed to cause a deflection on the recordings
- Poor spatial resolution (more sensitive to potentials generated on the cortex than to those generated in deep structures) and low signal-to-noise ratio
- Slow method since it requires the placement of a large number of electrodes
- Needs training for the patient, especially when related to muscular injury

3.3.3 Functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is a method that detects changes in blood flow in the brain using a strong and static magnetic field. fMRI is based on MRI, and it uses the special fact that brain blood flow and neuronal activity are associated [19]. It is based on the change in the magnetic properties of high-oxygen and low-oxygen blood as a measure. Normally, the results are shown as diverse colors representing the strength of activation of the different zones of the brain, as shown in Figure 3.6.

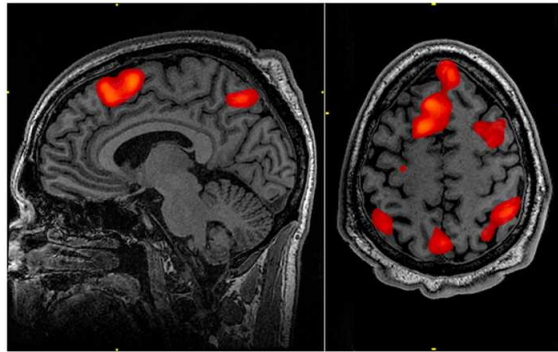


Figure 3.6: MRI scan during memory tasks



Figure 3.7: An MRI machine

This procedure is based on the fact that the main source of the energy's brain, glucose, is not stored inside the organ. When neurons fire, they need energy from glucose, which is transported to the brain by blood flows (2 mm next to the neural activity) that, at the same

time, bring oxygen. This difference in oxygen causes a reduction in the magnetic properties of the blood that reacts with the MRI process.

fMRI is used by neurologists to map the brain and evaluate treatments for patients with neural diseases or to detect depression, seizures, stroke, tumors, Parkinson's or Alzheimer's [20]. Moreover, in some studies, EEG recording and fMRI scans have been obtained simultaneously.

Advantages

- Can show how drugs move inside brain and show language and memory zones' activity.
- Can easily detect brain diseases
- Medium temporal resolution (seconds) and high spatial resolution
- Does not use any electrodes, noninvasive

Limitations

- Blood flow is an indirect marker of brain activity
- Does not show action potentials directly as an output
- Result images can appear with artifacts (noise)
- Can cause claustrophobia and is a risk for pregnant women
- Expensive, huge (1 ton), and loud high-pitch noise

3.3.4 Electrocorticography (ECoG)

Electrocorticography (ECoG), or intracranial EEG (iEEG), is a procedure that records electrical activity coming straight from the exposed surface of the brain. The electrodes are placed in the surface surgically, by incising into the skull with the help of EEG and MRI. Normally, they follow a grid or array configuration and they have a flexible design to uphold brain and head movements and not cause injury. Deeper structures activity such as the hippocampus can be recorded with the use of deeper electrodes. It uses the fact that neurons

are oriented perpendicular to the cortical surface and activity coming from a certain amount of neurons can sum to give a detectable signal. The output signals coming from ECoG are action potentials coming from neural synapses.

ECoG has been used since the 1950s to predict epileptic seizures. Nowadays, its use range has become wider by being applied, for instance, to aid amputees to control robotic arms.

Advantages

- Flexible placement of electrodes
- Can be done at any stage of a surgery
- Allows direct stimulation of the brain
- High temporal (milliseconds) and spatial resolution, with enough sampling time it can detect action potentials

Limitations

- Sampling time and spatial view limited by the area of exposed cortex
- Fully invasive, surgery and anesthesia can affect the recordings

3.3.5 Intracortical

This kind of signal acquisition is the most invasive. It uses single-cell electrodes (the deepest) to obtain single-neuron generated action potentials. Spikes recorded from neurons give multiple degrees of freedom and are the best signals for BCIs to use (highest spatial and temporal resolution, and high sampling rates). For example, the coding information of the brain in spike trains could be understood and used to improve BCIs. *Local field potentials* (LFPs) are also used in this kind of signal acquisition. LFPs are events happening in the same time in a huge amount of neurons (e.g. firing, change in synaptic potentials, somadendritic processes, etc.). Since they come from a lot of neurons, their spatial resolution is lower than that of a single neuron.

In Figure 3.8 it can be observed how deep an intracortical electrode is set in comparison to other technologies.

Advantages

- Highest time and spatial resolution
- Can detect single action potentials
- Less training and attention for the patient

Limitations

- Most invasive method, can cause local tissue infection/irritation due to surgical implantation
- Bad long-term stability of the signal acquisition over a long period of time



Figure 3.8: A diagram of the layers in the head, and the position of the signal acquisition electrodes depending on the technology used

	Cost	Invasiveness	Resolution	Type of measure
EEG	Inexpensive	No	cm	Neural oscillations
fMRI	Expensive	No	High	Blood flow (color zones)
ECoG	Surgery needs	Yes	mm	Action potentials
Intracortical	Surgery needs	Yes	.1 μ m	Action potentials

Table 3.1: A concise comparison between EEG, fMRI, ECoG, and intracortical characteristics

3.4 Signal Processing

The objective of the signal processing block is to extract important signal components from the signal acquisition block and translate them into commands for the BCI applications.

The feature extraction uses techniques to isolate interesting signal features (e.g., a neuron spike, EEG amplitudes) from the acquired signals. To be good features, they must be strongly correlated with the patients' intent. Another goal of feature extraction is to eliminate the noise generated by unrelated activity or outside of the brain (e.g., in EEG, moving muscles that have large amplitudes interfere and can be mistaken) that comes with the signal. After that, filtering methods are used to enhance spatial distribution. Examples: high-pass bipolar filter, surface laplacian, wavelets, windowing, periodogram, Fourier analysis, embedded algorithms.

Following extraction, the features are sent to the translation block, which converts them into commands for a BCI application that achieves the users' intent. For example, a patient trying to relax might create a decrease in power in a specific EEG wave and this could be translated as a selection of a letter or an upwards movement of a robotic arm. This block must also adapt to any changes and is highly dependent on the users' training. Examples include neural networks, hidden Markov models, linear and Bayesian classifiers. The operation of the device provides feedback for the user, and therefore closes the control loop.

3.4.1 Telemetry and signal transmission

An inductive link going through the skin provides all power and communication to neural prostheses or implantable BCIs. Two coils, one in the neural prosthesis itself, and the other on the outside of the body, form the induction link. The design of the link is set to comfort, geometric, and electrical constraints, and can be summarized in several steps:

- Take into account the coil and transmitter size and its physical constraints
- Find communication data rates and select right frequency adapting to the coil size
- Design according to power supply voltage and current specifications

- Specify the range of separation between coil and transmitter, for the link to be efficient

The typical range of operating frequency for neural prosthesis systems is 100 kHz - 50 MHz, taking into account that usually an inductive link works for both power and communication [15]. A coupling coefficient can be calculated depending on the space between the two coils. It is determined also by geometry of the coils and is a measure of the flux produced by the transmitter coil that gets to the prosthesis coil and computed as:

$$k = \frac{M}{\sqrt{L_p L_s}}$$

where M is the mutual inductance between the two coils, L_p the transmitter coil inductance (primary), and L_s the prosthesis coil inductance (secondary).

The critical coupling value is the number at which the reflection of the prosthesis coil resistance into the transmitter is the same as the transmitter's resistance, and is defined as follows:

$$k_c = \frac{1}{\sqrt{Q_p Q_s}}$$

where $Q_p = \frac{\omega L_p}{R_p}$ is the transmitters' quality factor, and $Q_s = \frac{\omega L_s}{R_s}$, is the quality factor for the prosthesis, R_p and R_s being the resistances of the transmitter and the prosthesis, respectively. To implement a circuit model of the system it is very important to obtain a reasonable estimate of the coupling coefficient. It is common to consider the electrodes as transducers and build equivalent circuits which include impedance representing the tissue, the electrode, and the microelectrode.

To control the stimulus parameters that the prosthesis produces to the brains, commands have to be provided, especially stimulus amplitude pulse and duration. The information rates in the link can be up to 1 Mbps, and sometimes need to be modulated, usually using amplitude-shift keying (ASK), frequency-shift keying (FSK), and phase-shift keying (PSK) modulation techniques.

3.5 BCI Commercial Applications

Neural prostheses can be separated in two general types: sensory and motor. Sensory prostheses often use an artificial sensor to replace the natural input that would come from

an ear or an eye. In the last decades, the cochlear implant has advance faster than, for example, a visual prosthesis. Motor prostheses electrically stimulate the neural-muscular system as a substitute of the brain or spinal cord, provoking the movement of the muscle and helping injured people. Although performing different tasks, sensory and motor prostheses design are normally similar.

3.5.1 Auditory prosthetics

Auditory prosthetics are devices that aim to restore partial or full hearing in deaf people. There are three main types: cochlear implants, auditory brain stem implants, and auditory midbrain implants. The first ones use electrodes implanted in the cochlea, the second ones stimulate the cochlear nucleus in the lower brain stem, and the third ones stimulate auditory nerves.

Cochlear implants (CIs) have been the most popular auditory implant with 324,000 people worldwide wearing them as of 2012 [21]. These devices are implanted through surgery, and might not cure deafness, but they can substitute for natural hearing and provide a sense of sound to the patients. Many subjects improved their hearing and speech understanding although the quality of sound coming from cochlear implants is less than natural hearing.

CIs are surgically implanted under the skin behind the ear and have an external and an internal part. A diagram of a CI is shown in Figure 3.9.

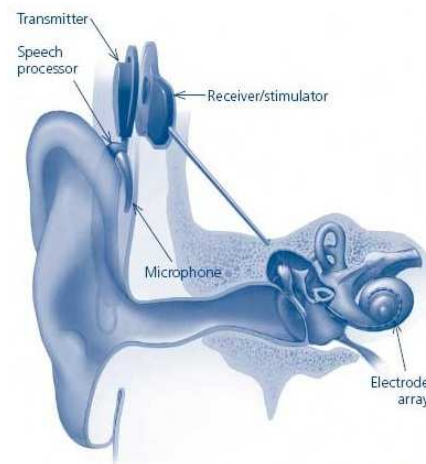


Figure 3.9: A diagram of an ear with a cochlear implant [21]

The external part includes a microphone that obtains sound from the environment and sends it to a speech processor which filters audible speech and sends it through signals to a transmitter. The transmitter is a magnet placed behind the ear that sends power and the sound signals through the skin to the internal receiver.

The internal part consists of a receiver which converts the signals into electrical impulses and transmit them to an array of electrodes placed on the cochlea. The electrodes send the impulses to the auditory nerves and then to the brain.

The microphone of the CI system receives sound from the external environment and sends it to a processor. The processor digitizes the sound and filters it into separate frequency bands that are sent to the appropriate tonotonic region in the cochlea that approximately corresponds to those frequencies.

The newest CIs allow patients to use them while swimming or even listen to music.

3.5.2 Visual prosthetics

Visual prosthetics are a kind of neuroprosthetics whose main objective is to provide partial or full vision for blind people. The idea of using electrical current to stimulate the retina and reconstruct vision comes from the 18th century (Benjamin Franklin). Visual prosthetics work better with subjects who suffer from visual degradation; even Braille could be read visually by a partially-blind patient, with the help of the retinal prosthesis shown in Figure 3.10 [22]. Visual prostheses are often inspired by cochlear implants.

A visual prosthesis consists of an implant in the retina or the visual cortex (invasive procedure) that is connected wirelessly from an external system that acquires the video images from the exterior. Then, the data is mapped to an analog signal in the implant, and delivered to the optic nerve through micro-electrodes, stimulating the optic neurons and creating an image in the retina or visual cortex of the patient. The procedure is shown in Figure 3.10

The amount of resolution of a visual prosthesis depends of the needs of the patient. For more quality of the image, more electron arrays should be implanted, and the wireless link should be improved, as well as the implant processor.

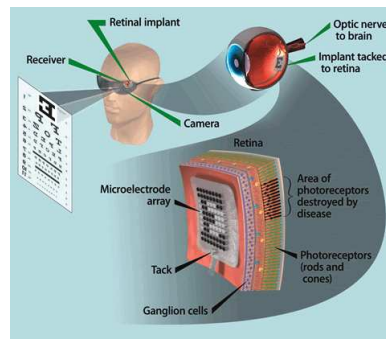


Figure 3.10: The Argus II retinal prosthesis system

3.5.3 Motor prosthetics

These devices are able to restore movement to people with motor disabilities such as sclerosis, paralysis, or tetraplegia. These prostheses work also with electrodes placed in the scalp that decode brain signals and send them wirelessly to the muscles that the brain is willing to move. This is due to the fact that the brain is able to generate the instruction, and the muscles are still active. The prosthesis just acts as the link.

Started by moving computer cursors, nowadays patients are able to move robotic arms or exoskeletons (built by researchers) just by thinking about moving them. This has been achieved by studying and classifying (filtering) the signals emitted by the patients in the implant processor. For example, the waveform of thought of opening or closing a hand is not the same as the one of moving a leg, bending a knee, or saying a word. The majority of motor prosthetics are robotic hands, arms, legs, and feet.

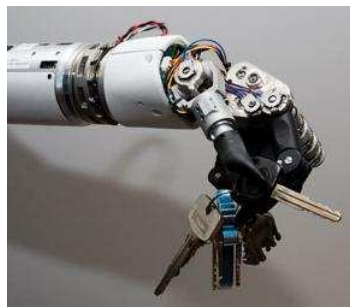


Figure 3.11: Dean Kamen's Luke Arm, world's most advanced motor prosthesis as of 2008 [23]

The focus of this thesis is not to have invasive prosthesis, that is, prosthesis that involve surgical implant of electrodes. The design example and simplified hardware demonstration in Chapter 6 involves only brainwaves via a bluetooth interface.

3.5.4 Cognitive prosthetics

Cognitive prosthetics seek to restore functionality that was lost in the brain tissue or the spinal cord due to damage, injury, or stroke. Some applications are: paralysis limb movement and control, bladder control, spinal cord injuries and pain relief, Alzheimer's and Parkinson diseases mitigation, speech deficits, brain traumatic injury, cursor movements, etc.

3.6 Concluding remarks

After reviewing neuroprosthetics we can say that this field is expanding enormously. It is a fact that neural prostheses have the potential of changing the lives of millions of people suffering from injury or diseases. The possibilities are infinite: a deaf person who can hear, a blind person that could see, an amputee could move a robotic arm, an epileptic attack could be prevented, and many more. The actual technology has helped a lot to make this possible. The depth presented by ECoG results has helped researchers to understand human cognition coming straight from real action potentials. EEG has expanded to many other fields like defense, security, video gaming, languages, and robotics.

However, there is still so much to be done. For example, reducing the invasiveness of the procedures, improving the implant's lifetime (reducing power consumption), developing prostheses able to learn from the brain's signals, and trying to understand how each body reacts differently to the implants, are ongoing efforts.

This field requires thorough collaboration between neuroscientists, engineers, surgeons and neurologists. It is a complex interdisciplinary field which challenges not only these professionals but also more fundamental understanding of biophysics, molecular biology and medicine. In the design process, electrical engineers must understand and translate signals that are composites of many activities at the cell level.

In the next chapter, we will focus on the motor activities that allows the proper design of prosthesis for movement of arms or legs. From these signals, a proposed design of an autonomous brainwave controlled prostheses is demonstrated in Chapter 6.

CHAPTER 4

From neurons to nerves to muscle

In order to design and implement a motor neural prosthesis, one must understand how the communication between brain and muscles is accomplished. How do we move? What nerves are involved? What signals are transmitted? How to move the muscle of a patient that is paralyzed? These are some of the questions that are addressed over the next sections. Understanding the properties of the nervous-locomotive systems gives better insight for diagnostic and solution of neuromuscular diseases. And, for the neuroprosthesis design engineer, this is the fundamental basis for the interface of the human body with hardware.

In this chapter we perform a review of the nervous system, the muscles, and electromyography.

4.1 The nervous system

The part of an animal's body that send signals to control voluntary and involuntary actions of the different parts of its body is the *nervous system*, the size of which is approximately 100 cells and 1000 billion cells in worms and humans, respectively. The nervous system works through the entire human body. Its internal structure was not well understood until it was examined using a microscope. In 1906, Spanish Nobel Prize winner Ramón y Cajal was the first to describe the morphology and connecting processes of the nerve cell (*neuron*), defined and explained in Chapter 2.

Nerves, however, are the axons of neurons that grow from the brain and the spinal cord and branch repeatedly forming fascicles from the tip of the head to the tip of the toes. Nerves “communicate”: they rely on sensory receptors that sense changes happening inside and outside of the body, they decode the gathered information and what to do with it, and they finally send the instruction message coming from the brain to the organ or muscle of

destination. They also let us sense (through the five senses) and give us the sensation of pain.

The nervous systems consists of two main parts in vertebrate species: the *central nervous system* (CNS) and the *peripheral nervous system* (PNS), which are depicted in Figure 4.1.

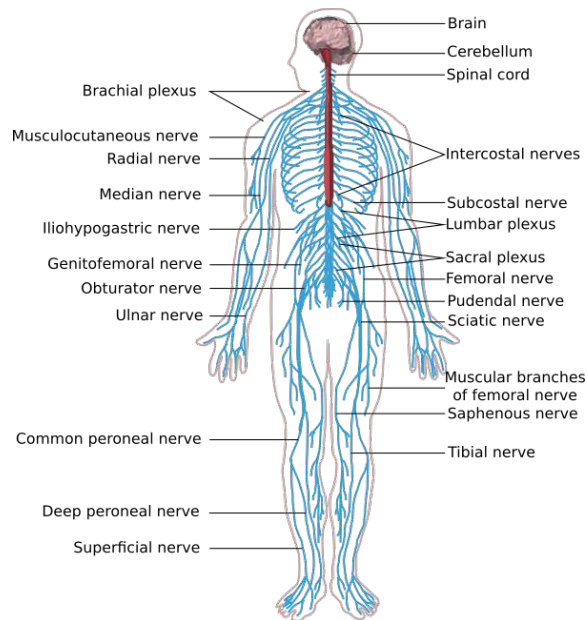


Figure 4.1: The nervous system composed of the CNS (red) and the PNS (blue) [24]

4.1.1 The Central Nervous System

The main role of the central nervous system is to be the “commander” of the body: to give orders, to coordinate, to send instructions in the form of electric signals from the brain to the rest of the body and to receive feedback. The CNS is composed of the brain and the spinal cord. The brain controls everything: movements, thoughts, speech, memory, and reflex movements. The spinal cord is connected to the brain and is protected by the vertebral column. It has 31 pairs of spinal nerves, which are the connection between the brain and the PNS. The basic unit of the CNS is a neuron. The main injuries in the CNS are due to genetics, intoxication, and stroke.

How the CNS works is essentially explained via the neuron firing mechanisms as described in Chapter 2. We will not go any further than already has been described as the CNS is not a main issue for the motor autonomous prosthesis problem.

4.1.2 The Peripheral Nervous System

The rest of the nerves in our body that are not in the CNS define the peripheral nervous system. In the PNS, the nerves are grouped forming fibers of axons, reaching to all parts of the body. The PNS will relay the orders coming from the CNS back out to the body. It is divided into two parts: the motor division and the sensory division. The motor division gathers the outgoing messages coming from the CNS and carry them to the limbs and organs, and the sensory division collects the impulses from the sensory receptors (skin, muscles, organs) and takes them to the CNS.

Peripheral nerves present a complicated axonal transport system that conducts the electrochemical action potentials as well as nutrients and other substances. The action potential transmission works in a similar way as in the brain, with an intracellular current flowing from a positively charged area to a close-by negatively charged area. A current also flows in the opposite way, provoking the exchange of ions, depolarizing the membrane up to a threshold and thus causing the transfer of the action potential. The amplitude of the action potential follows Ohm's Law, large nerves with a great number of fibers generate larger currents. If they have a big square diameter they will present a big resistance.

4.2 Muscles

The term *muscle* is derived from the Latin *musculus*, which means “little mouse”, because some muscles contracting look like mice moving under the skin [25]. Muscles are a soft tissue that can be found in most animals below the skin, most of them attached to the bones. They are in charge of the locomotion of the body, remaining posture, processing food through the digestive system and moving internal organs (like the contraction of the heart).

Muscle cells have protein filaments that slide producing the contraction or expansion of the muscle, changing both the length and shape of the cell. Muscles use the oxidation

of carbohydrates and other chemical reactions as energy. They are often classified in three types:

- *Skeletal*, which mostly move due to voluntary commands and are attached to the bones by the tendons. In this thesis we focus in this type of muscle.
- *Cardiac*, which are involuntary moving muscle that are found in the walls of the heart (myocardium). Cardiac muscles need calcium ions from the outside so that cardiac contractions happen. The action potentials are fired by the exchange of sodium and calcium ions. They also rely on the blood with oxygen and nutrients delivered to the heart.
- *Smooth*, which are involuntary moving tissues that can be found in the walls of blood vessels, the uterus, the urinary bladder, respiratory and digestive tract, and the skin. Most of the smooth muscles are single-unit, meaning that the muscle either contracts or relaxes.

4.2.1 The Skeletal Muscle

The *skeletal muscle* is a striated muscle under the voluntary control of the somatic nervous system (a part of the PNS). It belongs to one of the big three types of muscles (skeletal, cardiac, or smooth) that exist in the human body. Most of the skeletal muscles are related to movement and locomotion, and are attached to the bones through tendons.

A diagram of the different components of a generic skeletal muscle is shown in Figure 4.2.

The skeletal muscles are formed by individual muscle cells, often called muscle fibers (myocytes), which are filament-shaped and grouped into fascicles. Fiber lengths are 50 μm on average in a human adult. At the same time, muscle fibers are made up by myofibrils, which are composed by myosin filaments, which are made up by sarcomere units (basic unit of the fiber). The sarcomeres are the basic of the muscle contraction.

A *motor unit*, explained in detail in section 4.2.3, is formed by a single motoneuron and all the fibers reached by its axon.

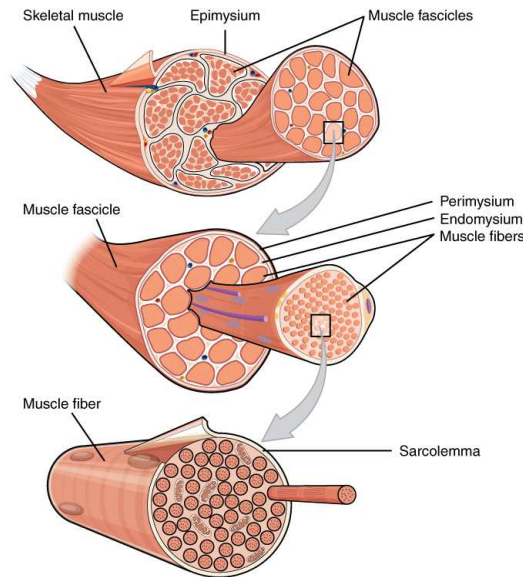


Figure 4.2: A muscle diagram showing its different components [26]

A disease related to skeletal muscles is called *myopathy*, and occurs when muscular fibers do not function properly, causing muscular weakness, stiffness, or spasm.

4.2.2 The Muscle Cell Membrane

The muscle cell membrane is similar to that explained in Chapter 2. It is the boundary between the cytoplasm and extracellular fluids and the base of the generation of the EMG signal explained in section 4.3. There is a higher concentration of potassium and lower concentration of sodium and chloride with respect to the extracellular fluids. The relation shown by the Nernst equation in Chapter 2 holds.

The electrical potential in human skeletal muscle cells is of -90 mV, ranging from -20 mV to -100 mV from one tissue to another. The difference with a nerve cell is that in the muscle the force produced occurs when calcium ions are released. Also, the membrane has different layers and parameters from those of a nerve cell. The tubular system or T-system are tubules oriented into the fibers that form a path for current flows that take the action potential from the outer membrane (excitation of contraction). However, for simplicity, most of the neuroscientists use the Hodgkin and Huxley model explained in Chapter 2 as a first approximation to a model of the muscle cell membrane due to its bioelectric activity

(ion channel) representation. Understanding the dynamics of the action potentials becomes very important in surface EMG, especially distinguishing their duration, amplitude, times of initiation, and velocity of propagation (3 - 5 m/s) can give insight into analyzing muscular diseases such as myopathy or neuropathy.

4.2.3 The Motor Unit

A *motoneuron* is a neuron whose cytoplasm is located in the spinal cord and whose fiber is extended outside the spinal cord to indirectly control organs or muscles. They are classified in three types: alpha, beta, and gamma. A muscle fiber can receive several action potentials when a muscle is contracted, whereas a single motoneuron may reach several muscle fibers. This is the way a motor unit was defined by Liddell and Sherrington in 1925 [27]: a motor unit consists of an axon and the few hundred muscle fibers that it supplies. Nowadays, the motoneuron is also considered a part of the motor unit. All muscle fibers in a motor unit are of the same fiber type. Table 4.1 shows the different number of muscle fibers and motor units for several muscles of the body.

Muscle	No. of Fibers	No. of MU	Fibers/MU
Ext. rectus	27,100	2,970	9
Plastyma	2,970	1,096	25
1st lumbrical	10,038	96	108
1st dorsal interosseous	40,500	119	340
Brachioradialis	129,100	333	410
Tibialis anterior	10,500	445	562
Gastrocnemius	1,120,000	579	1,934

Table 4.1: The number of fibers, motor units, and fibers per motor unit in several human muscles [28]

When a motoneuron fires it produces the contraction of all muscle fibers that are reached by its axon. Motor units are the smallest functional element of contraction in the body, and they work together to cause the movement of a muscle. The force with which a muscle is moved is determined by the number of motor units that take part in the muscle contraction.

The principles of motor control are shown in Figure 4.3. Instructions for movement travel from the motor cortex to the α -motoneurons of the spinal cord which at the same time, have direct control of the motor units of the muscle the patient wants to move. The summation of all input-commands received takes place at the α -motoneuron, whose potential reaches a certain threshold and causes the firing of the *motor unit action potentials* (MUAP) and the activation of the different motor units that cause the muscle contraction. The MUAP can come from a single fiber or from two to hundreds of fibers.

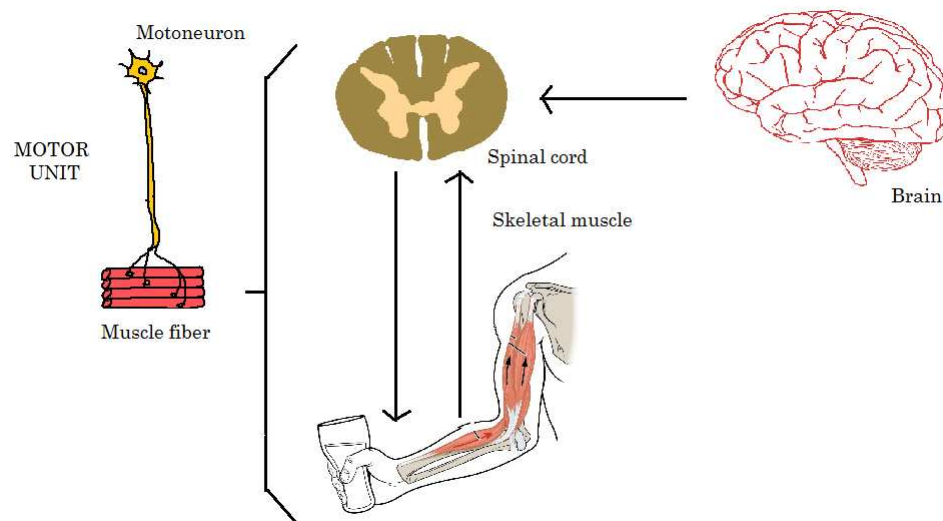


Figure 4.3: A diagram showing the elements that take part in motor control, modified from [29]

4.3 Electromyography

Electromyography (EMG) is a diagnostic medicine technique that measures the electrical activity generated by skeletal muscles. An electromyogram is a representation of the electrical potential generated by the muscle cells when they are active. It gives insight into the integrity of the entire motor control system: motoneuron, neuromuscular junction, and muscle.

EMG is used for identifying neuromuscular diseases and disorders of motor control. It is also used in control of neuromuscular prostheses that replace hands, arms, and legs. Three

different electromyograms are shown in Figure 4.4, one from a healthy patient, one from a patient with neuropathy, and one with a patient with myopathy. Muscle action, contraction, diseases, and fatigue influence the shape of the signal.

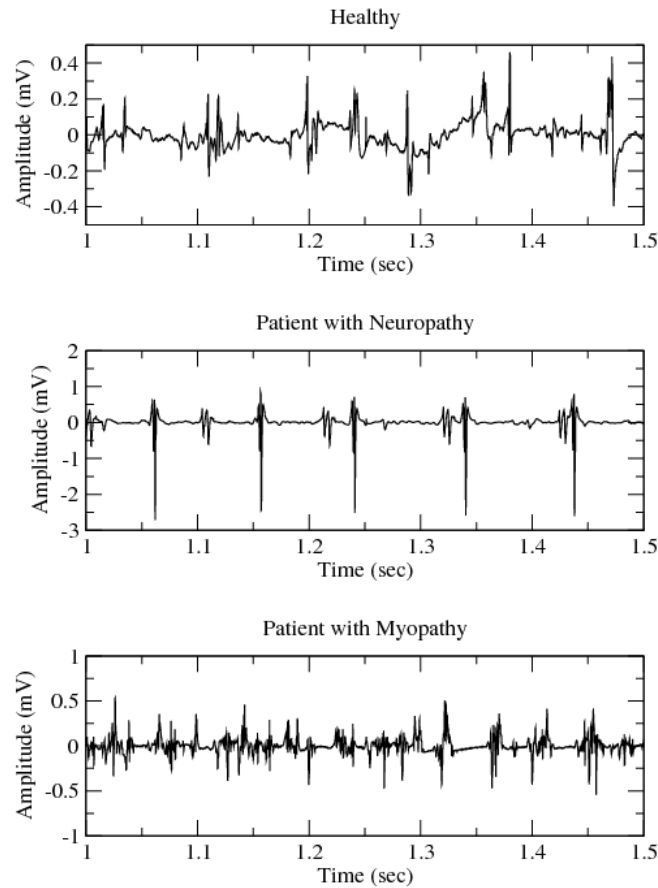


Figure 4.4: : healthy, with neuropathy, and with myopathy

How the signal is acquired (types of electrodes) may influence the diagnosis. In the next subsection, the most important electrode techniques used today are explained.

4.3.1 Electrodes

The electrodes used for capturing the EMG signal are very similar to those shown in Chapter 3. They present similar issues for design (size, tissue damage, timelife of the device, stimulation, invasiveness, and injury risk). As stated before, the EMG signal recorded is influenced by the type of electrodes used. In this section we conduct a review of the surface

electrodes, which add the activity from several motor units; needle electrodes, which are able to record MUAPs, and single fiber needle electrodes, which record *single fiber action potentials* (SFAPs). Less commonly used are the multielectrodes, the flexible wire electrodes, and the microelectrodes placed inside muscle cells.

4.3.1.1 Surface EMG

Surface EMG is a non-invasive technique for recording an EMG signal. It is based on the electrolytic conduction between the surface electrode and the skin (chemical balance). The addition of all currents generated by the motor units current flows from the superficial muscle to the electrode. These electrodes have an average surface area of 1 cm^2 and they are very easy to implement on the patient's skin since they do not require medical supervision. They are placed on the skin with the help of adhesive tape, because if the electrode moves from its position the signal gets distorted. Also, a stimulator is short-circuited to the electrode or ground in order to produce a stimulus. The skin is cleaned with alcohol and electrolyte cream is applied in order to reduce the impedance of the zone. A sketch of the placement of a surface electrode is shown in Figure 4.5.

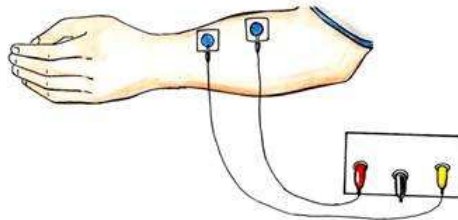


Figure 4.5: A sketch of the placement of a surface electrode [30]

Surface EMG works well for monitoring muscle contraction, motor behavior, neuromuscular activity, sports evaluations, fatigue of the muscle, and motor prostheses. This technique records the summation of the contributions from the different motor units (MUAPs). The amplitude of the EMG is an indicator of the number of available motor axons (it can be used to diagnose myopathy), and its latency shows the conduction time of the fibers.

Nevertheless, these electrodes are not good for studying a single MUAP (which has high-frequency components) since they record under a radius of approximately 20 mm compared to the 500 μm that can be achieved with a needle electrode. Because of this, it is more challenging to interpret surface EMG, however, its simplicity has contributed to applications made by nonmedical operators (engineers, students, professors), such as motor prostheses or fatigue evaluation [31].

4.3.1.2 Needle EMG

The needle electrodes, as used in EEG, can be also used for EMG recording. Although they are invasive and need medical supervising, they can detect activity from small muscles when surface recording false. A concentric needle electrode, of 25 mm in length, has a recording surface area of 0.03 mm² [32]. It can detect MUAPs located within about 500 μm to 1 mm radius from the tip of the needle, which reveal changes in localized internal structure of the motor unit. A surface electrode is set at the same time, working as a ground reference.



Figure 4.6: An example of a needle electrode: the Ambu® monopolar EMG needle [33]

The placement of a needle electrode can be hard, depending on which muscle is selected and its size. The way the needle is set can influence the accuracy of the EMG, the ideal place to set the needle is the longitudinal midline. Then, the needle is then moved to multiple spots within a relaxed muscle to evaluate both insertional activity and resting activity in the muscle. Besides, needle EMG involves the voluntary activation of the muscle, and hard to cooperate with for infants or patients with paralysis due to invasiveness.

Needle EMG is indicated when there is pain in the limbs and weakness from spinal nerve [34].

4.3.1.3 Single Fiber EMG

This technique requires a much smaller and sharper needle electrode than the standard one used to record signals coming from individual muscle fibers. It can be as small as 25 μm in diameter [35]. Single fiber EMG may record abnormalities occurring within individual axons, like the delay between contraction of the fibers within a motor unit. It tests diseases of the neuromuscular junction caused by drugs or intoxication, something that would be impossible to record with surface EMG. With this technique, the SNR is improved by 4 times and the amplitude of the action potential increases by 2 times, a resolution that gives good insight to the electromyographer. The loss amplitude of a SFAP could indicate a problem of axonal loss.

4.3.2 Assessment and Equipment

A MUAP is created by the discharge that a motoneuron produces on the cell membrane of the muscle cells that its axon innervates (motor unit). The waveform of a MUAP depends on the number of fibers present in a motor unit, as well as on the distance between the muscle cells and needle/surface electrode.

When assessing EMG, clinical personnel visually inspect the form of the raw EMG signal or the MUAP (thanks to EMG decomposition, explained in section 4.3.3, or to needle electrodes) of the muscle at rest on an oscilloscope or a computer. Studies are repeated with a few different motor units to compare the average result with reference values. Abnormalities can be determined easily by observing the amplitude, duration, area, and phases of the MUAP. The peak-to-peak amplitude shows the number of active fibers of a motor unit and might be an indicator of myopathy when it is decreased.

Then, they inspect the signal obtained during voluntary contraction of the muscle, repeating the studies by setting the electrode in different locations in distances of a few mm in the muscle.

Researchers have to take into account that the resistance of the muscle tissue and its temperature, the type, size, and location of the electrode, the percentage of muscle voluntary contraction, the electrical properties of the amplifiers, the filters used processing the data, and the sensory noise can influence in the resulting signal too.

The equipment that is used nowadays with EMG consists of a stimulator, a differential amplifier, an antialiasing filter, an A/D converter, and a computer interface (Figure 4.7).

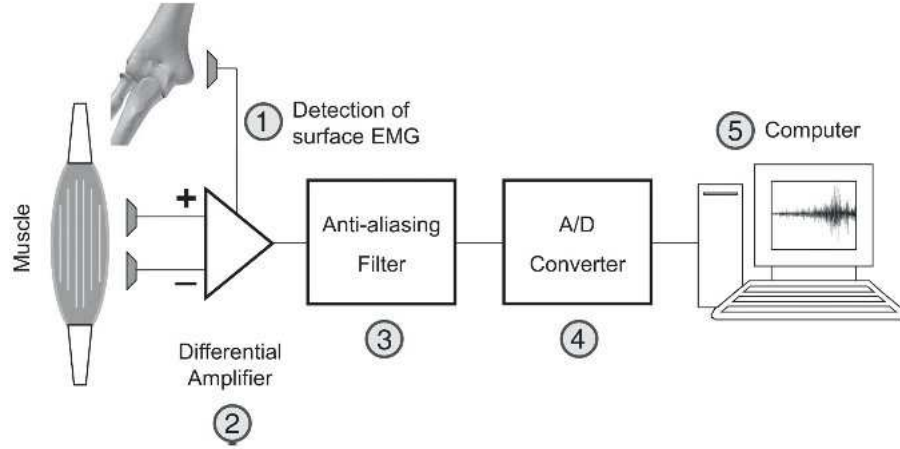


Figure 4.7: A diagram of the equipment used in a typical EMG study [36]

The differential amplifier calculates the signal difference of the two points where of detection, and increases the weak, raw voltage and current result into a suitable signal for the analog-to-digital conversion. After the amplifier, the signal goes through an anti-aliasing filter and an A/D converter to be displayed on an oscilloscope or a computer. Most of the times the filtering and A/D conversion is done by the computer itself. The interface on the computer can also include commands for further processing such as noise filtering, frequency analysis (FFT), gain tuning, and diagnostic programs. The electrical stimulator is also controlled by the computer, receiving feedback at the same time.

4.3.3 Modeling

Rosenfalck [37] approximated the *intracellular action potential* (IAP) as the smallest potential inside the muscle cell, that propagates through the sarcolemma. This was done due to the necessity of a simpler model without membrane biodynamics such as the Hodgkin and Huxley model. He considered a muscle fiber as a very thin cable with current flowing axially, and, applying the cable equation, derived that the transmembrane generated current is proportional to the second spatial derivative of the IAP [29]. Nandedkar and Stålberg were the first ones to simulate a MUAP in 1983 [38].

Dimitrov and Dimitrova [39], in 1998, modeled a SFAP as the convolution of the first derivative of the IAP and an impulse response

$$\varphi(t, x_o, y_o) = C_{\text{an}} \frac{\partial(IAP(t))}{\partial t} * \frac{1}{v} IR(t), \quad (4.1)$$

where C_{an} is the coefficient of proportionality and is defined as

$$C_{\text{an}} = \frac{d^2 K_{\text{an}} \sigma_i}{16 \sigma_{\text{an}}}, \quad (4.2)$$

where d is the fiber diameter, K_{an} is the anisotropy ratio, $\sigma_{\text{an}} = \sqrt{\sigma_x \sigma_y}$ is the tissue conductivity, and σ_x and σ_y the conductivities along the x and y axis, respectively.

$IAP(t)$ can be approximated as

$$IAP(t) = A_1 t^{A_2} \exp(-A_3 t). \quad (4.3)$$

$IR(t)$ is

$$IR(t) = \frac{1}{r_{\text{an}}} = \frac{1}{\sqrt{(x_o - vt)^2 + K_{\text{an}} y_o^2}}, \quad (4.4)$$

where v is the conduction velocity in m/s, and x_o and y_o are the horizontal and vertical distances to the electrode in mm.

With the parameters defined by Dimitrov and Dimitrova for a typical IAP shape $A_1 = 21242$; $A_2 = 4.8133$; $A_3 = 14.033$, and for the IR $x_o = 20$ mm; $v = 4$ m/s; $K_{\text{an}} = 5$; $y_o = 0$ mm, an IAP and an IR are plotted in Figure 4.8 and Figure 4.9, respectively, using the simulator from Chapter 5.

So, a SFAP will depend on the conduction velocity, the diameter of the fiber, and the relative position of the fiber to the tip of the electrode. An SFAP with the same parameters is plotted in Figure 4.10.

In 2001, Stashuk [40] showed the composition of an EMG signal.

Using surface EMG, the summation of all fibers SFAPs in a motor unit (a MUAP) is detected. So he defined the MUAP of the j th motor unit as (Figure 4.11)

$$MUAP_j(t) = \sum_{i=1}^{N_j} SFAP_i(t - \tau_i) s_i, \quad (4.5)$$

where τ_i is the temporal offset of each SFAP, N_j is the number of fibers in the j th MU (size of the MU), and s_i is a binary variable representing the neuromuscular junction that indicates if the fiber i is firing or not. The waveform of the MUAP will vary depending on the delays of the potentials, changes on the position of the electrode, or a singular fiber failing to fire.

In order to keep the force generated by a muscle, motor units have to fire repeatedly. When it happens, the MUAPs generated by a MU separated by their discharge intervals are called a *motor unit action potential train* (MUAPT) and are defined as (Figure 4.12)

$$MUAPT_j(t) = \sum_{k=1}^{M_j} MUAP_{jk}(t) \delta_{jk}, \quad (4.6)$$

where $MUAPT_j(t)$ is the MUAPT of the j th motor unit; $MUAP_{jk}(t)$ is the MUAP generated during the k th firing of the j th motor unit; M_j is the number of times the j th motor unit fires; δ_{jk} is the k th firing time of the j th motor unit.

Then, the EMG signal will be the summation of the MUAPTs of all motor units (Figure 4.13)

$$EMG = \sum_{j=1}^{N_m} MUAPT_j(t) + n(t), \quad (4.7)$$

where $MUAPT_j(t)$ is the j th MUAPT; N_m is the number of active motor units; $n(t)$ is the background instrumentation noise. A diagram of the complete process (used in Chapter 5) is shown in Figure 4.14.

The reverse process (the separation of an EMG signal into its MUAPTs) is called EMG decomposition. De Luca and Mambrito [41] in 1984, were the first ones to propose an EMG signal decomposition model. The decomposition is useful when a needle EMG is not available, since in this way the assessment of single MUAPs can be performed.

Some unique characteristic of the waveform that is common to the MUAPs of the same type must be identified in order to detect different MUAPS. Besides, to classify them as coming from the same MU, they must be more alike than the other MUAPs, and have to occur several times in the EMG signal. Stashuk [40] stated that a good decomposition should deal with signals having the following characteristics:

1. five or more MUAPTs

2. non-stationary MUAPs shapes
3. variable MUAP shapes due to variability in the operation of neuromuscular junctions and background biological noise due to the activity of other motor units
4. two or more motor units with similar MUAP shapes
5. frequent superpositions of MUAPs
6. non-stationary motor unit firing pattern statistics
7. intermittent recruitment and decruitment of motor units.

Typically, a bandpass filter is applied to remove noise and unnecessary repetitions. After that, the MUAPs are classified via a vector for pattern recognition and clustering algorithms, normally using features as peak-to-peak voltage, number of phases, duration, number of phases, or Fourier coefficients. After that, the corrections and updates of an expert may be needed to achieve 100% accuracy. The results could be used in the diagnosis of neuromuscular diseases and motor unit physiology. There exist automatic EMG decomposition algorithms such as the one provided by EMGLAB software [42], shown in Figure 4.15.

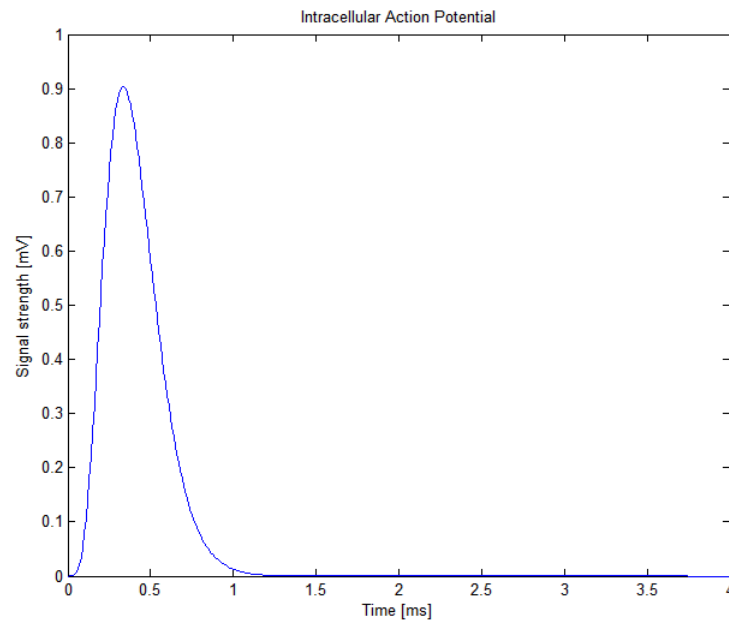


Figure 4.8: A typical IAP shape

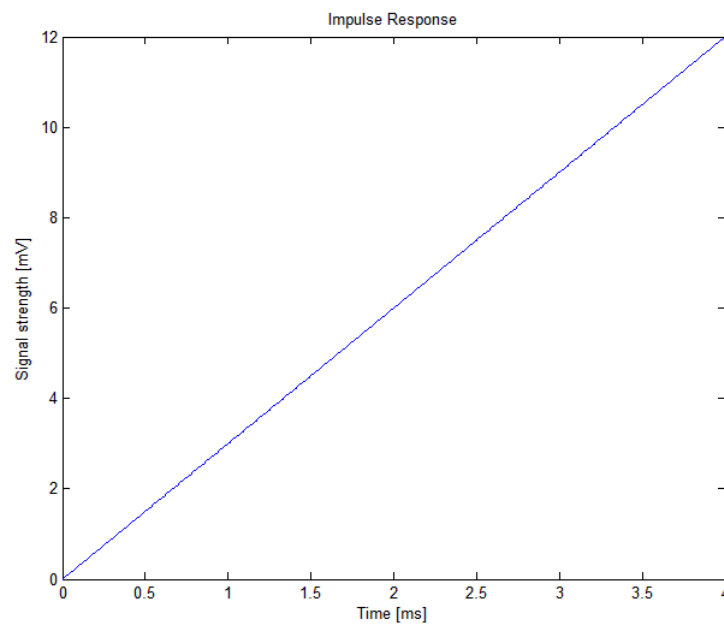


Figure 4.9: A typical IR shape

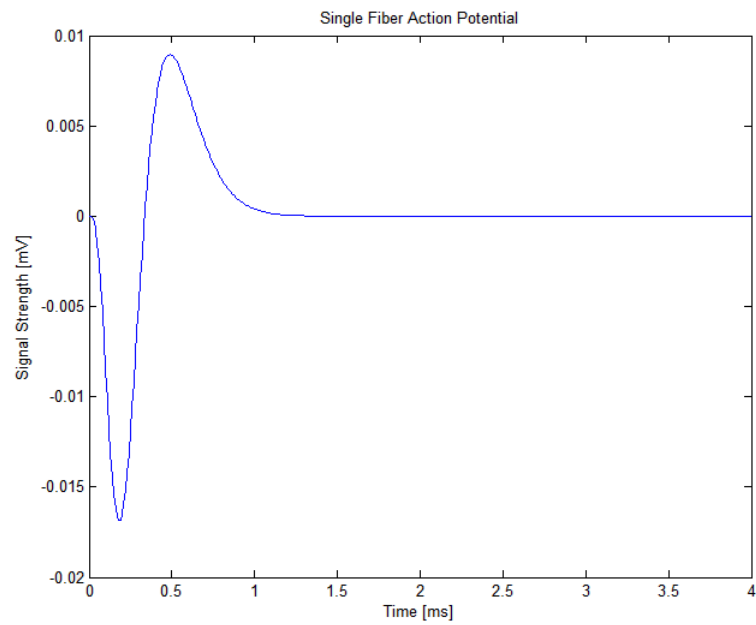


Figure 4.10: A SFAP

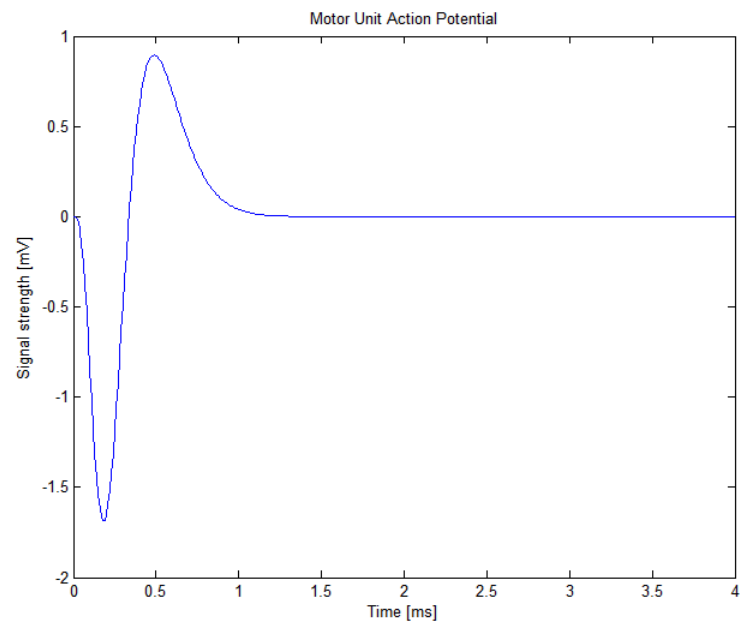


Figure 4.11: A MUAP

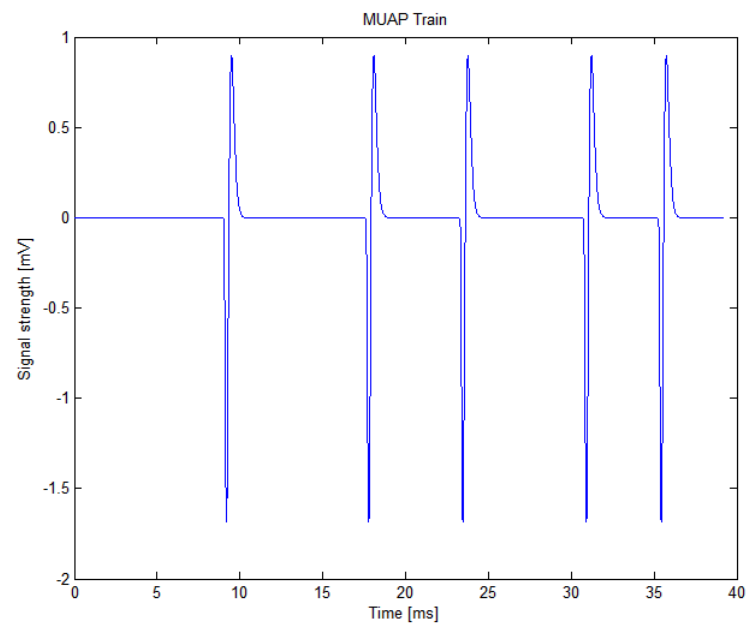


Figure 4.12: A MUAPT (5 repetitions)

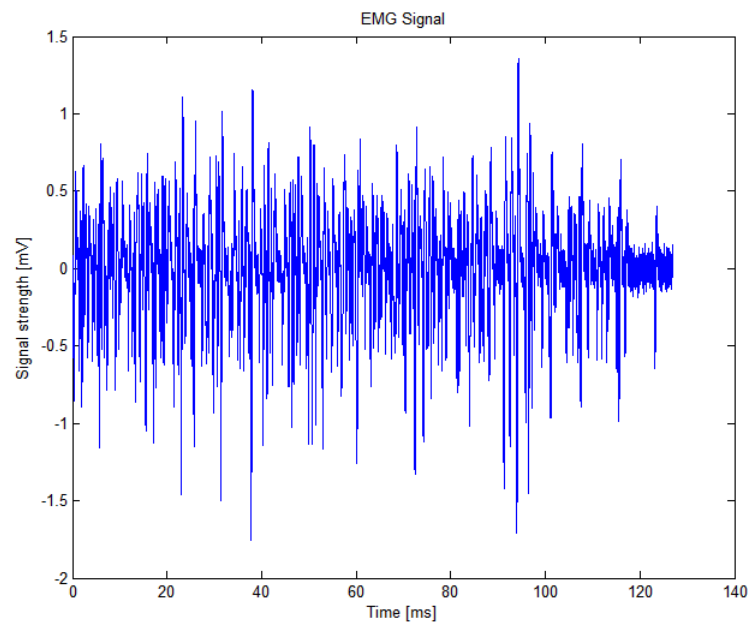


Figure 4.13: An EMG signal

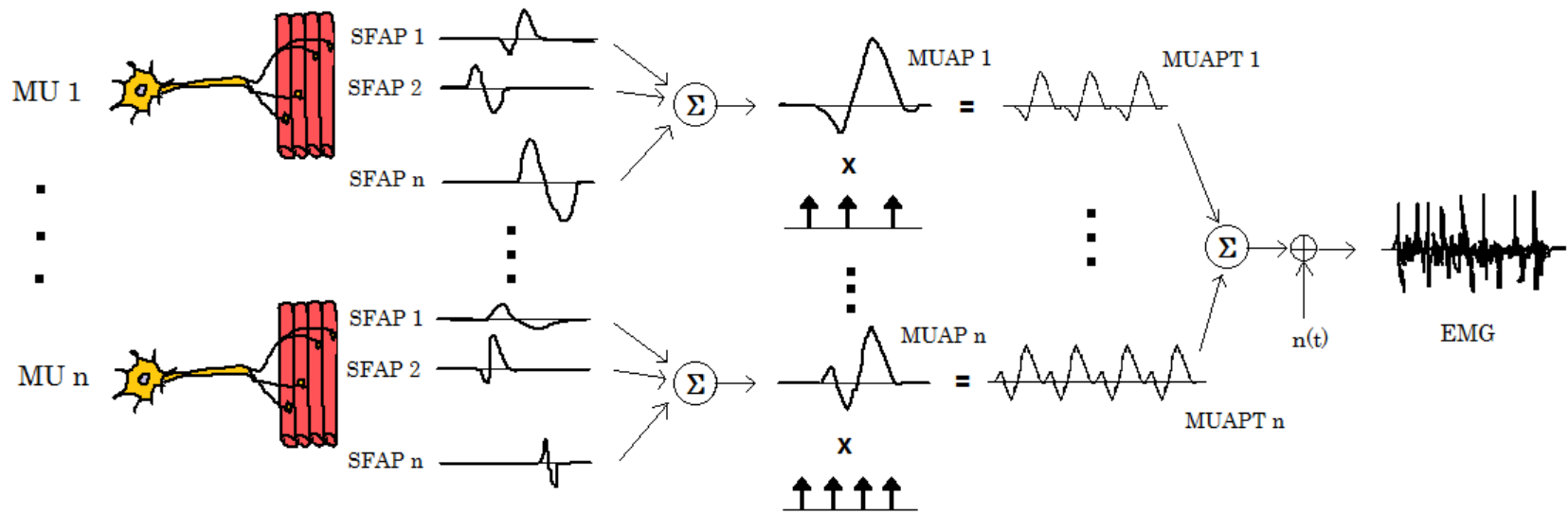


Figure 4.14: A diagram of the EMG composition

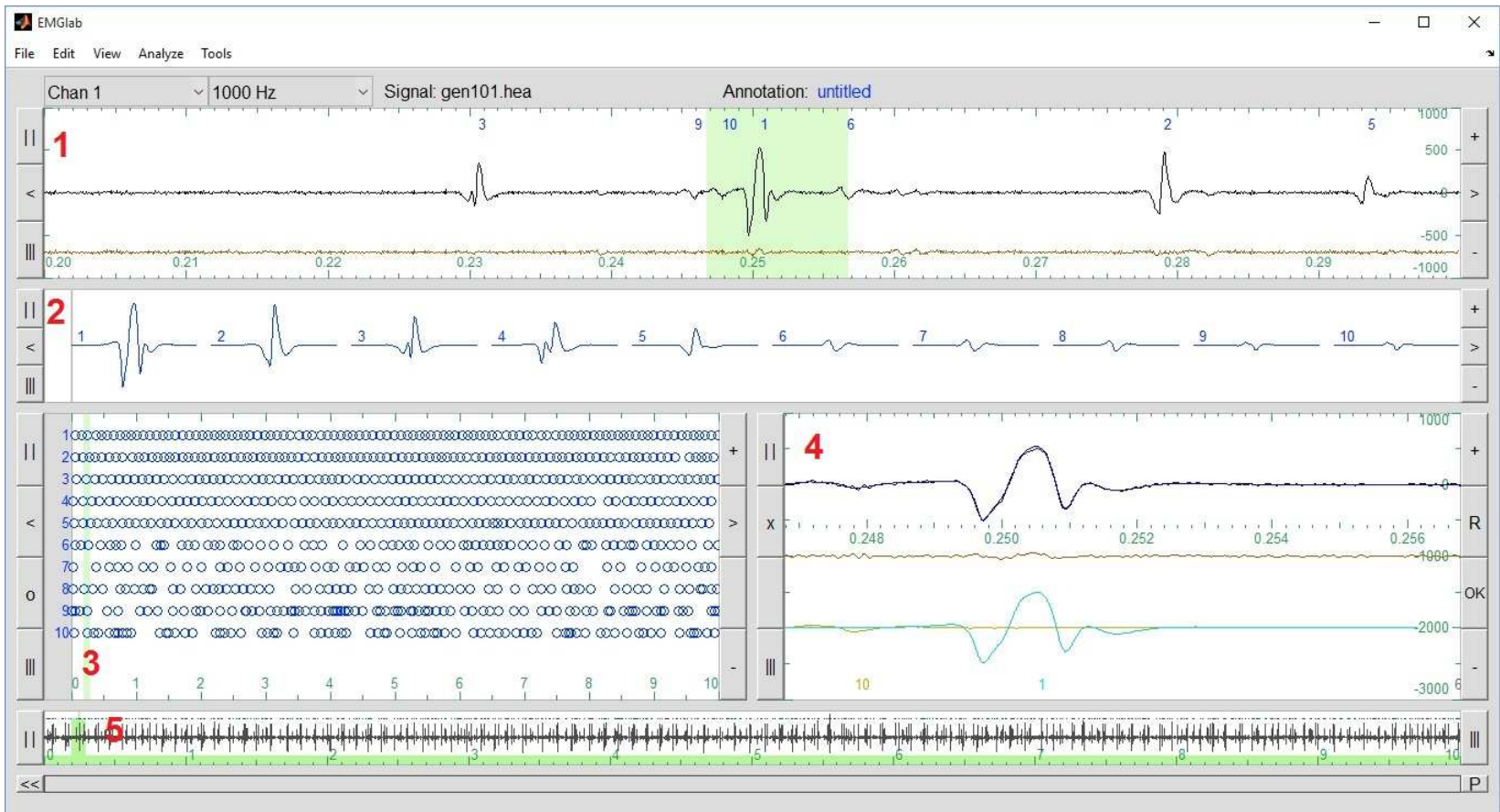


Figure 4.15: EMGLAB decomposition. Panel 1 shows the zoomed EMG signal and its MUAPs numbered. Panel 2 shows the EMG decomposition in its MUAPs (10 in this case). Panel 3 shows how many times each MUAP appears in the complete signal. Panel 4 is for assessment, MUAPs can be dragged here in order to create a new one of if some MUAP detection is missing. Panel 5 shows the complete EMG signal.

CHAPTER 5

Design and simulation methodology in muscular prostheses development

The main work of this thesis is shown in this chapter. Using the EMG model shown in the previous chapter, the expected signal is first calibrated from a healthy source. Then, the autonomous prostheses would be linked by a code that translates brainwaves to the more complex actions of real nerves. Thus, the EMG would have to have an interface from a “composite” signal like brainwaves, to neuromotor action. This is a very difficult problem to implement.

In this chapter we focus on the EMG signal generation and simulation. We then demonstrate the full scope of what must be considered to implement the design. In the next chapter, a simplified “toy model” of an autonomous arm prosthesis is described in some detail and demonstrated with simple operating hardware.

5.1 Basic design of an autonomous prosthesis

We have to remember that the goal of a prosthesis is to aid patients with injury or disease to have a life as normal as possible. A basic design of a limb prosthesis would be based on the diagram in Figure 5.1.

1. When the system needs to be initialized, an EMG model from the simulations in Section 5.2 is loaded into the computer as a reference.
2. The computer is the main element in the configuration of the prosthesis since it is the processor and the translator of the EMG signal into the movements of, in this case, the prosthetic robotic arm.

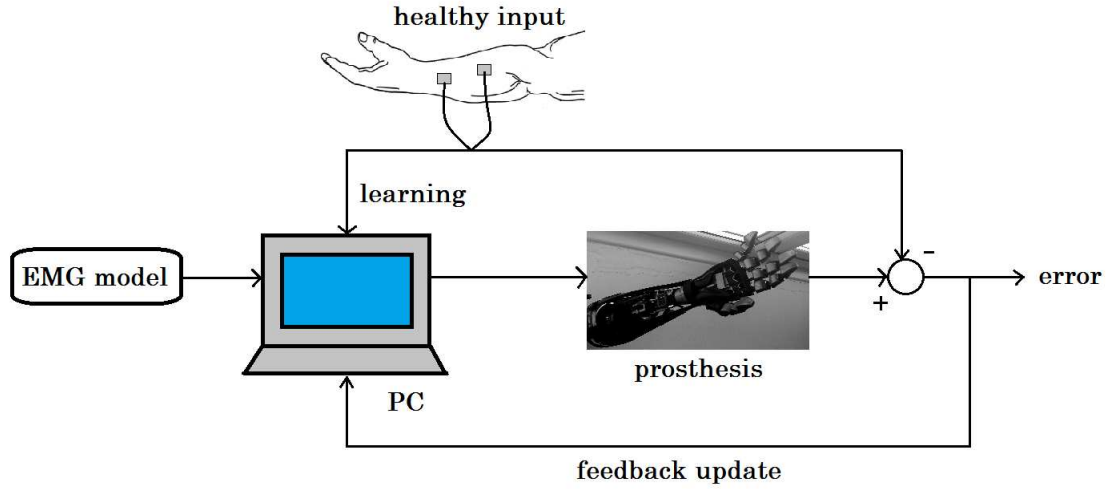


Figure 5.1: A diagram of a basic prosthesis control. Prosthetic arm modified from [43], healthy input modified from [44]

3. The computer also receives the input surface EMG signal coming from a healthy arm, in order to learn and improve the model and give more accurate signals to the prosthesis.
4. This input signal is also subtracted from the EMG signals given to the prosthesis to compare and get the error.
5. This error is fed back to the computer to keep updating and improving the model until stable movements similar to the healthy arm would be achieved.
6. Unhealthy arm inputs could be added to the model in order to improve the model and convert them into healthy signals to transfer to the prosthesis.

5.2 Simulation model for signal generation

Inspired by the EMG simulator done by Hamilton-Wright [45], we have built an EMG simulator following the Dimitrov and Dimitrova model and the signal composition procedure from Stasuk, both explained in Chapter 4. The program was built in MATLAB, using the Graphics User Interface (GUI) shown in Figure 5.2.

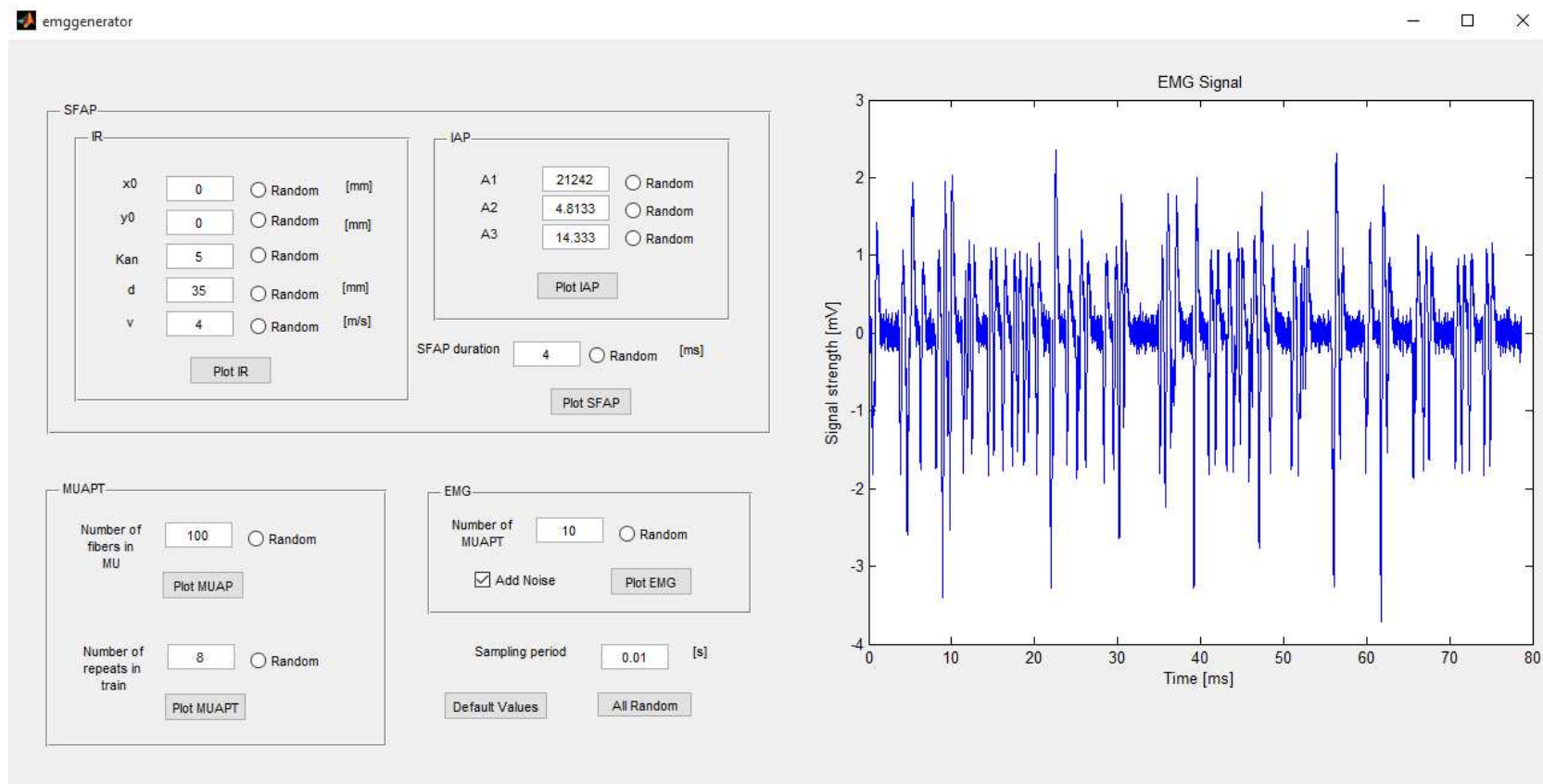


Figure 5.2: The GUI of the EMG generator, with default values and added noise

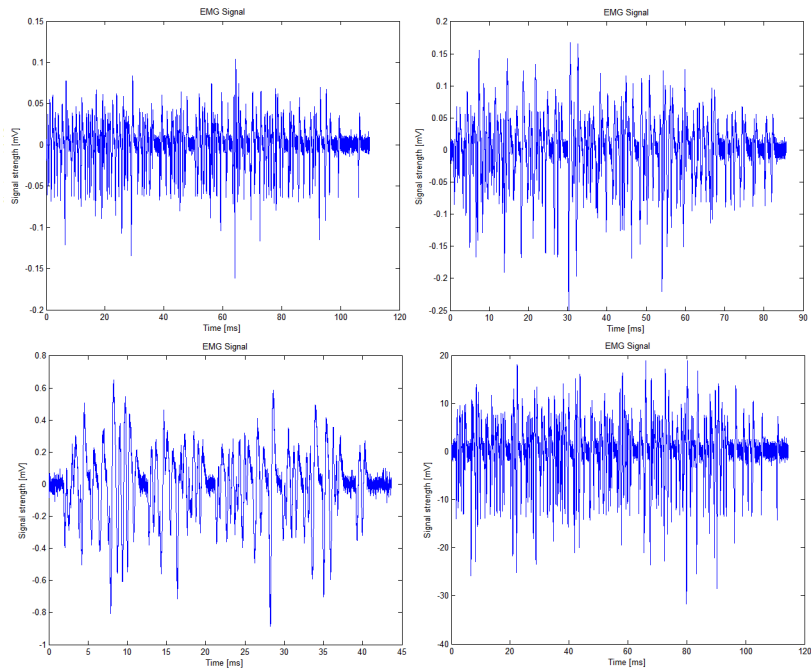
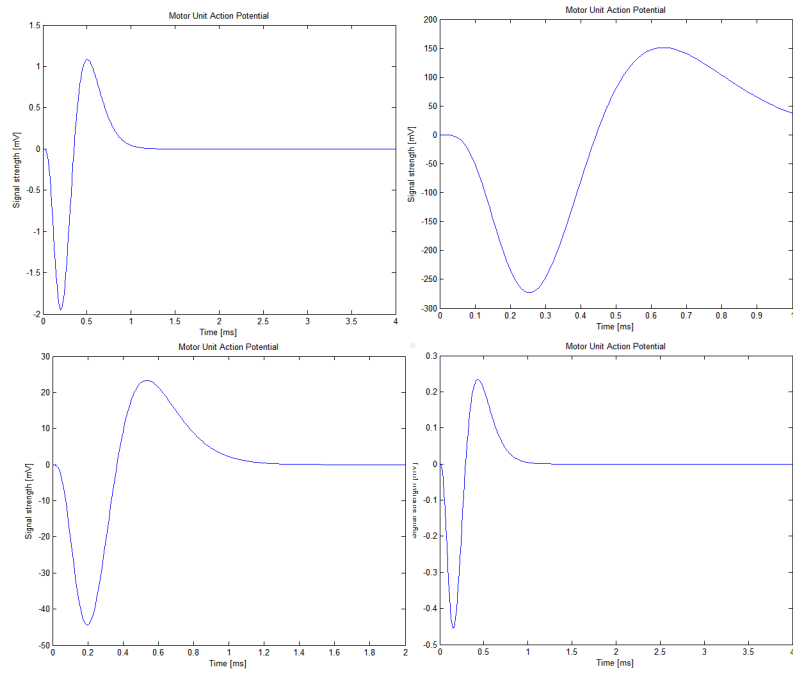
As shown in the GUI, the SFAP panel includes the IR panel and the IAP panel. The user can plot the IR (Impulse Response), as well as the IAP. The values of x_o , y_o , K_{an} , d , v , A_1 , A_2 , and A_3 can be changed or a random value can be chosen when the random option next to the value is selected. The default values (shown in Figure 5.2) and random ranges for the IR and IAP are set according to [39] and [46]. The chosen random ranges are: $x_o = [20 - 40]$ mm, $y_o = [20 - 40]$ mm, $K_{an} = [4 - 6]$, $d = [25 - 40]$ mm, $v = [3 - 5]$ m/s, $A_1 = [20000 - 25000]$, $A_2 = [4 - 6]$, $A_3 = [11 - 16]$. The user can also plot the SFAP, which is the result of the convolution of the first derivative of the IAP and the IR.

The MUAPT panel gives the option to choose how many fibers the Motor Unit is going to have. Again, the value can be changed or chosen randomly between 80 and 120 fibers, and a MUAP can be plotted. In the same panel, a MUAPT can be plotted after choosing the number of times the MUAP is going to be repeated in the train. This value can also be chosen randomly between 3 and 15 repetitions.

In the EMG panel, one can choose the number of MUAPTs that are going to generate the EMG signal, or if the EMG signal is going to show the instrumental noise or not. This value can also be chosen between 5 and 25.

Finally, there are two buttons that set all values to default, or all values to random. The sampling period of the signal can also be changed.

One of the main objectives of this application is to show that, as in Chapter 4, an EMG signal depends strongly on all the parameters shown in Figure 5.2: the relative position of the electrode, the anisotropy ratio, the diameter of the fibers, the conduction velocity, on how is defined the IAP, the number of fibers in each MU, the number of times each MUAP is repeated, and the number of MUs. One can show this by selecting all random values and plotting several signals in Figure 5.3 and Figure 5.4. A diagram showing the dependence on these parameters is shown in Figure 5.5.

Figure 5.3: Generated EMG signals using the *all random* commandFigure 5.4: Generated MUAPs using the *all random* command

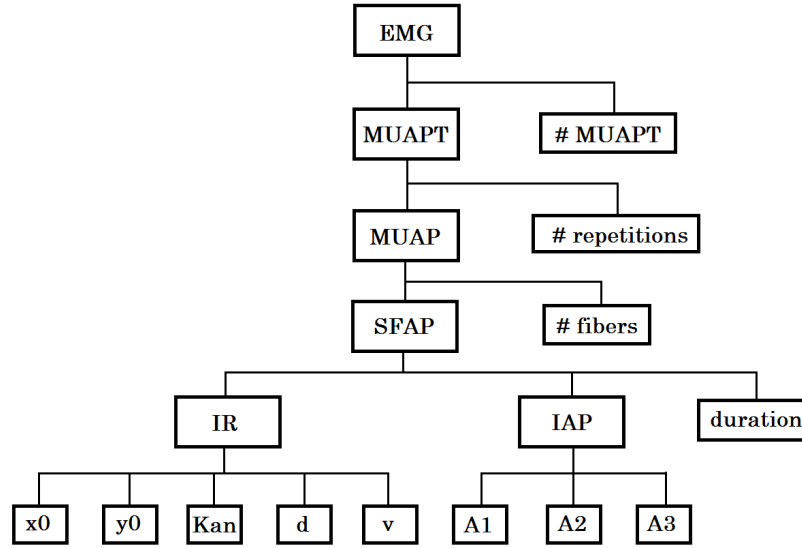


Figure 5.5: The parameter dependence of EMG signal

5.3 Real test case application considerations

When thinking of taking the design and simulations and applying it to a real case (building a real muscular prosthesis), many issues appear that any engineer and electromyographer have to take into account. While designing the prosthesis and even when simply recording EMG signals, several considerations have to be taken into account:

- *Type, shape, and location of the electrode.* As explained in Chapter 4, having a surface or needle electrode has its advantages and limitations, which have to be considered. For example, needle may cause damage to muscular fibers. The size, shape, and location of the electrode matters too, that is why often studies are repeated with different electrode locations and insertions, to get more reliable results.
- *Number of Motor Units and number of muscular fibers.* A signal will not be the same depending on the number of MUs and motor fibers in the MUs recorded by the electrode. Also, different muscles contain different MU and fiber quantities as shown in Chapter 4.
- *Instrumental noise.*

- *Filter application and type.*
- *Signal decomposition model used and its accuracy.* For surface EMG and decomposing the signal into its respective MUAPs, the model for decomposition and its accuracy have to be taken into account. Sometimes, the hand of an expert is needed to complete a model's decomposition.
- *Behavior of the patient.* While in session, surface EMG patients are more receptive (non-invasive method). Needle electrodes cause discomfort, especially for children and elderly and this may cause bad signal recording.
- *Several other parameters* like the ones shown in Table 5.1.

Description of the parameter (symbol)	Default value
Radius of muscle compartment (R_c) (mm)	38
Radius of fat + muscle compartment (R_b) (mm)	39
Volume conductor radius (R_a) (mm)	40
Volume conductor length (L_v) (mm)	200
Conductivity of muscle compartment, axial ($\Omega \text{ m}^{-1}$)	0.5
Conductivity of muscle compartment, radial ($\Omega \text{ m}^{-1}$)	0.1
Conductivity of fat compartment ($\Omega \text{ m}^{-1}$)	0.05
Conductivity of skin compartment ($\Omega \text{ m}^{-1}$)	1.0
Muscle fibers belonging to one motor unit	200
Muscle fiber conduction velocity (m/s)	3.125
Mean fiber length (L_F) (mm)	100, S.D. = 20
Electrode array distance (L_E) from mean endplate position (mm)	20
Mean end plate position (E_P) (mm)	0, S.D. = 10
Mean tendon position (mm)	± 50 , S.D. = 10
Sample frequency (Hz)	2000
Muscle fiber depth (D_F) of MU#1 (mm)	3–5; 3–13
Difference in depth (d) between MU#1 and MU#2 (mm)	1–10

Table 5.1: Parameters to be considered when simulating and designing muscular prostheses [47]

In the simulator in Section 5.2, one could simulate EMG signals coming from actual large muscles just by changing the number of fibers and number of MUs, but it would take hours for the program to generate the signal. We have to remember from Chapter 4 that, for example, the *Plastyma* muscle has 2,970 fibers and 1,096 MUs. However, using more powerful computational languages like C++ this could be used to simulate EMG signals

and compare them to real signals acquired from patients. Even myopathic or neuropathic signals could be generated.

5.4 Concluding remarks

We conclude this chapter with the satisfaction of fully scoping the design effort developing the code for the EMG. We are, however, limited in two points which can be expressed by the limitations of a Master's Thesis and the available equipment.

First, developing the Brainwave to EMG code is outside the scope of this work. Such efforts, as shown in a recent DARPA program which is extensively explained in Chapter 6, involves a much bigger effort.

Second, the autonomous arm is in itself a huge effort to build and requires expensive mechatronic subsystems.

However, this thesis goes beyond just scoping the design effort and simulating the muscle action from neuronal signals. In the next chapter, a simplified design showing three degrees of freedom autonomous open loop arm is demonstrated.

CHAPTER 6

A demonstration of a 3-state brainwave controlled robotic prosthesis

6.1 Arm prostheses state of the art

To understand the demonstration of Section 6.2, we need to understand the big picture in terms of upper-limb prostheses. In this section we review the state of the art in arm prostheses: myoelectric prostheses and mind-controlled arm prostheses.

6.1.1 Myoelectric upper-limb prostheses

People who endure paralysis or amputation have an impediment to have a quotidian life. The most popular solution to the problem of limb/movement restoration nowadays are myoelectric prostheses.

Myoelectric prostheses are externally powered limb prostheses that use surface EMG to control limb movements. After the patient intends to move the desired muscle with a certain intensity, a controller translates the EMG signal into speed and strength commands to be sent to the prosthesis. For instance, if a hand was lost, the patient has to move the forearm extensors corresponding to the movement to open and close the hand. Elbow flexions and shoulder movements can also be achieved with this technology. The prosthesis is often connected to the body through a custom simple socket that creates suction.

The technology behind the translation of EMG signals to commands is pattern recognition, learning and classification. The distinguishing EMG patterns can be used to identify different intended movements and implement them in the prostheses.

One example of the where researchers are now in the field of myoelectric prostheses is the prosthesis attached to an amputee trucker in at Chalmers University in Sweden in

2014 [48]. This prosthesis was attached to the bone, with a direct link to nerves and muscle of the patient, right at the elbow. Data goes through the wires to and from the arm and the patient gets feedback, stimulating peripheral nerves he even got a sense of touch. The patient was followed during one year, still working as a truck driver did not present any difficulties to perform daily life situations. Even better, he showed better motor control and more range of motion, compared to socket prostheses.

6.1.2 Mind-controlled prostheses

Mind-controlled prostheses are the future for people who are completely paralyzed. The field is evolving quickly, one example is DEKA's Luke Arm.

The DEKA Arm, often named as "Luke Arm", due to Luke Skywalker's bionic arm in *The Empire Strikes Back*, was built in 2014 by DEKA Research and Development Corp., and created by inventor Dean Kamen. This project received \$40 million as funding from US Defense Advanced Research Projects Agency (DARPA), as part of its Revolutionizing Prosthetics program.

The DEKA Arm is a noninvasive device that can perform simultaneous movements, and its hand can mimic six different grips control its grasp. The presentation video was a US Army veteran using his brain to control the prosthetic arm to scale a rock-climbing wall. So this shows how powerful this prosthesis is, which has been able to peel a grape or handle a drill. To perform all the movements, DEKA added wireless switches on the user's feet that controlled multiple joints simultaneously.

The ability to feel touch through this prosthesis was also built. A blindfolded volunteer with spinal cord injury stated that it felt just like his own hand being touched. This was achieved via torque sensitive sensors and connecting electrodes in the sensory cortex of the patient that were connected to the prosthesis. The device also uses EMG signals for quality assurance.

After years of development and testing, Luke's Arm has been approved for commercial use by the FDA. Now the challenge will be to find a manufacturer to convert this prosthesis into a cost-affordable device for the big public [49] [50].

Another example would be the control of a prosthetic arm via a BCI [51]. In this case, a patient paralyzed 10 years agreed to undergo surgery and receive a brain implant. The difference with previous experiments with other paralyzed patients was that this time the electrode was implanted in the posterior parietal cortex, a region related to planning movements, instead of the primary motor cortex. After focusing on the object he wished to grab, the BCI recognized his goal in less than 200 ms. After 2 years of training and teaching the BCI has managed to play rock, scissor, papers almost 7000 times and used the prosthetic arm to drink beer from a bottle.

6.2 Demonstration of a brainwave controlled prosthesis

The control of three different movements of a robotic arm with the use of just the mind was achieved. To acquire the brain signal (EEG) a NeuroSky® MindWave Mobile device was used, and a robotic arm (prosthesis) was built using Lego Mindstorms NXT. The devices were connected via MATLAB, using NeuroSkyLab and the RWTH Mindstorms Toolbox. A GUI was built in MATLAB to process the waves and produce the movements of the robotic arm.

6.2.1 The NeuroSky® MindWave Mobile

Every thought creates an electrical discharge (brainwave) that can be measured by EEG (electroencephalogram). The brainwaves in our mind are classified according to frequency ranging from 0 to 100 Hz (Delta, Theta, Alpha, Beta, and Gamma). Mental states like attention or relaxation (result of a huge number of electrical discharges) can be measured with several non-medical devices. Alpha waves (8 – 12 Hz) are related to relaxation, and Beta waves (12 – 40 Hz) are related to concentration [52].

The NeuroSky® MindWave Mobile is the first EEG-reading device able to communicate via Bluetooth™, meaning that it can connect with any device that supports this technology (iOS, Android, or computer) without using any wires [53]. Several apps come with this device, through which a person can observe how their own EEG waves change,

burn a barrel when focusing, make a disco ball float when relaxing, or blowing fireworks with blinking (Figure 6.2).

A MindWave Mobile headset is shown in Figure 6.1. This device amplifies the raw brainwave signal and filters the noise [54]. The two main parts in the headset are the sensor in the forehead, which is a surface EEG electrode, and the attachable clip to the ear lobe, which makes the body voltage the same as the headset (ground/reference). Thus, it is crucial that these two connections are properly fit for a good EEG signal reading.



Figure 6.1: The NeuroSky® MindWave Mobile [55]

6.2.1.1 MindWave Mobile outputs

- *Raw EEG signal.* With a sampling frequency of 512Hz, the raw EEG signal is detected by the electrode in the forehead in a 16-bit signal, and can be decomposed in Delta, Theta, low Alpha, high Alpha, low Beta, high Beta and Gamma waves.
- *Attention eSense.* It is an indicator that describes indicates the user's level of mental "focus" or "attention", which refers to high intense concentration. Its value ranges from 0 to 100. Values from 1 to 20 are considered low, and may indicate distraction or anxiety. Values from 20 to 40 are considered reduced, and from 40 to 60, neutral (baseline). From 60 to 80, they are considered slightly elevated, and from 80 to 100, they are elevated (high intense concentration). A value of 0 means that the device has been unable to calculate the eSense value (poor signal). One can focus by simply staring at a single object, calculating math, maintaining a single path, etc.

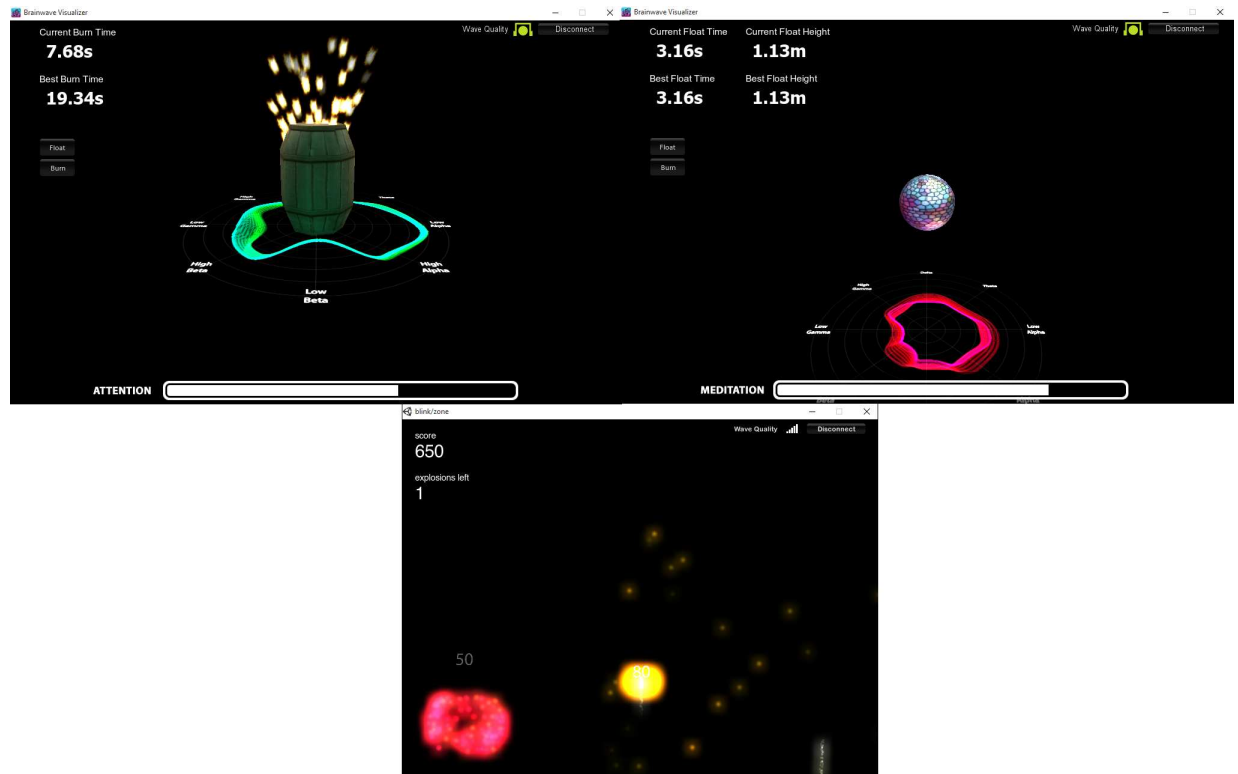


Figure 6.2: Several apps included with the MindWave Mobile

- *Meditation eSense*. It is an indicator that describes indicates the user's level of mental "calmness" or "relaxation". Its value ranges from 0 to 100. It is needed to be noticed that this indicator refers to a person's mental levels, not physical levels, although relaxing the muscles can help one to get mentally relaxed. A person can mentally relax by closing the eyes, clearing the mind, taking a deep breath, etc. The values of the eSense work in the same way as the Attention values.
- *Blink strength*. It is an unsigned one byte value that reports the intensity of the user's most recent eye blink. Its value ranges from 1 to 255. The higher the intensity of the eye blink, the higher the number will be. It can also be observed in the raw EEG signal [56].

6.2.2 The robotic arm

The robotic arm was built using the Lego Mindstorms NXT 2.0, Education Base Set.

LEGO Mindstorms NXT is a programmable robotics kit released by LEGO. The main component in the kit is a brick-shaped computer called the NXT. It can take input from up to four sensors and control up to three motors, via a modified version of RJ12 cables, very much similar phone cords. The brick has an LCD display and four buttons that can be used to navigate a user interface. It has microcontroller with FLASH memory and RAM, and USB and Bluetooth support. It also has a speaker and can play sound files at sampling rates up to 8 kHz. Power is supplied by a Li-Ion rechargeable battery and charger. Complicated programs and sound files can be downloaded using a USB port or wirelessly using Bluetooth. Files can also be copied between two NXT bricks wirelessly, and some mobile phones can be used as a remote control [57].

The final version of the robotic arm used in the demonstration was built following the instructions in [58], and is shown in Figure 6.3. Three motors are connected to the three output pots of the NXT brick, each of which performing a task described in Section 6.2.3.

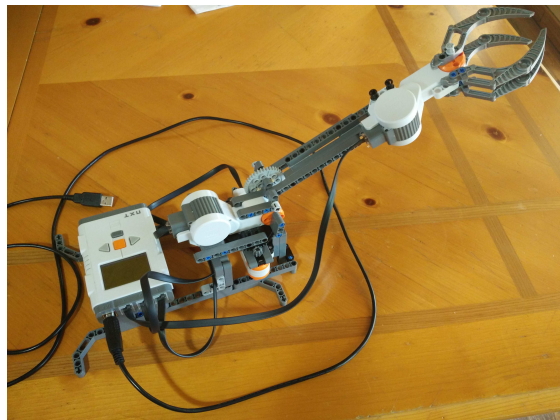


Figure 6.3: The robotic arm

6.2.3 Operation and communication

The communication between the was achieved starting from a MATLAB script built by NeuroSky® called NeuroSkyLab. NeuroSkyLab is able to record and plot EEG data recorded in MATLAB using any NeuroSky® headset [59]. The NXT was connected to the computer via USB, and controlled with the RWTH - Mindstorms NXT Toolbox for MATLAB [60]. This toolbox allows the user to establish a connection with the NXT and to program and control

the robotic arm. The NeuroSkyLab script was modified in order to connect the MindWave Mobile and the NXT at the same time, and convert into the GUI shown in Figure 6.4.

The GUI plots the attention eSense, the meditation eSense, the raw EEG signal detected by the electrode, and shows some simple graphic instructions to the user. In this way, a demonstration of a 3-state mind-wave controlled robotic arm was achieved (thresholds can be changed):

- When focusing (attention eSense greater than 70), the robot arm moves along the vertical axis (elbow), and waits 20 seconds for the user to stop focusing and be able to realize the movement when focusing again.
- When relaxing (meditation eSense greater than 75), the robot arm moves along the horizontal axis (elbow), and waits 20 seconds for the user to stop relaxing and be able to realize the movement when relaxing again.
- When blinking, the claw closes. When blinking again, the claw opens (grabbing).

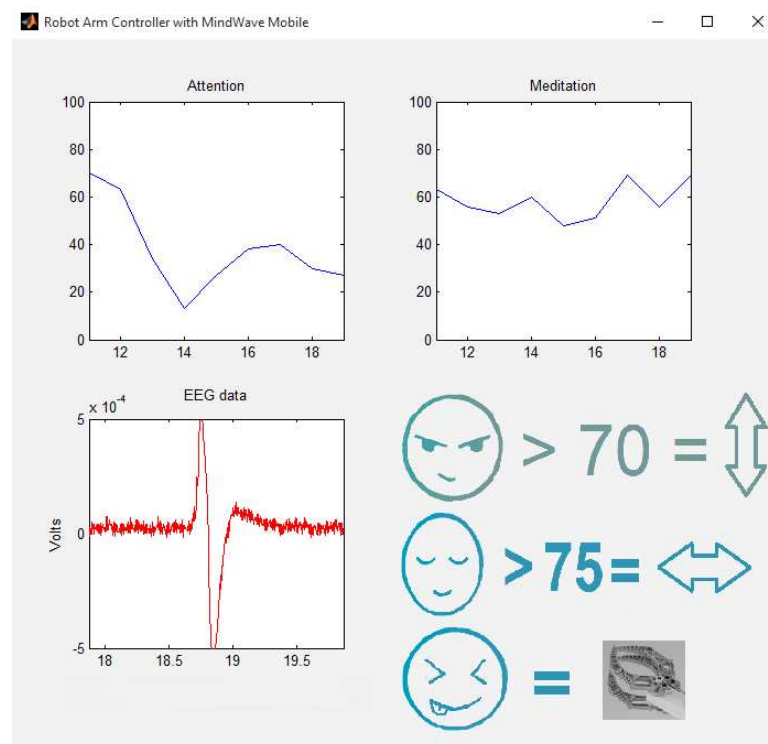


Figure 6.4: The GUI of the Robot Arm Controller, showing a blink in the EEG plot

CHAPTER 7

Conclusions and future work

In this thesis we first presented a summary of neurons and their classical models. We studied the biology and physiology structure of neurons: synapses, soma, axon, dendrites, and neurotransmitters. We showed the most important unit of neural communication in the body; the action potential and its shape. The most important classical neuron models were explained; namely the membrane potential and the Nernst equation, which introduced the Hodgkin and Huxley model. In the HH model, which uses four differential equations, we can see represented in a circuit all the biodynamic changes that take place when a neuron fires an action potential. The Morris-Lecar model, the reduction from four dynamic variables to two, and the phase-plane dynamics which it afforded, helped us to understand the FitzHugh-Nagumo model, which, based on the van der Pol oscillator, represents the same dynamics of the HH model but with only two differential equations: a cubic and a linear model. This model is used to generate action potentials in a more systems oriented way.

Second, a review of the actual neuroprosthetics panorama was performed, starting with its history since the 1960s until today. The concept of Brain-Computer Interface was introduced. A BCI restores or improves the interactions of the brain with the environment. The elements that form a BCI were studied: signal acquisition (and types of electrodes used) via EEG (most used, cheap and noninvasive), EcOG (invasive but precise), fMRI (noninvasive but expansive and loud), and intracortical acquisition (invasive and most accurate); and signal processing and transmission. Examples of BCI applications like auditory, visual, or motor prostheses helped us to understand the rapid expansion of the BCI development

Chapter 4 is focused on understanding the brain-muscle relationship by explaining the nervous system, which is divided into the CNS and the PNS. How the muscle works, specially the skeletal type, was studied in depth in preparation for chapter 5. Insight at the skeletal muscle was brought by studying its components: the muscular cell membrane (very similar

to a neuron's membrane but with its singular peculiarities), the muscle fiber, and the motor unit. This had to be done to comprehend how a muscle moves. Then the technology of electromyography was explained. EMG is, in summary, a muscle movement translated into a signal, and through its inspection and its decomposition into MUAPs, clinicians can diagnose if a disease is present in the muscle where the signal is recorded.

Discovering EMG generation modeling was useful to come up with the simulator of chapter 5 which, at the same time, gave us an idea of how to design a muscular prosthesis. Trying to export the basic design of chapter 5 to the real world, we realized that it is not that easy. A lot of parameters have to be taken into account and a lot of work needs to be done, especially if in the future the priority will be to design autonomous prosthesis. We focus on the EMG simulation since the code needed to send to the prosthesis the desired movements as if generated by the brain. But, the code from brainwave to EMG, we restrained from studying in this thesis because that would be another thesis in itself.

Finally, we wanted to give a little bit of information on the state-of-the-art in autonomous arm prostheses controlled with by brainwaves. We know the potential this field has, and how it can help paralyzed and amputees. We wanted to show a basic example of a prosthesis control by using elements that were within our reach: a low-cost biosensor able to read EEG and an easy-building robotic arm using the kit from the lab course *Introduction to Robotics* at UCCS (a LEGO robot kit). In doing so, we could at least append to the design considerations of chapter 5, a hardware implementation that demonstrate the brainwave-to-hardware connection.

This work allowed us to learn in fields not strictly related to a Master's program, like biology, neuroprosthetics, medicine, neuroscience, and robotics. But it also was useful to use the concepts learned during the program: circuits, modeling, signal processing, control, and simulation. It is, in a sense, a "real world" situation where engineers must understand, in new industries such as neuroprosthetics.

We also realized that neuroprosthetics and mind-controlled robotics are fields of studies where engineers have a really important contribution, but we are not forgetting medical doctors, clinicians, neuroscientists, biologists, physicians, physiotherapists, etc. Only working together and interconnecting disciplines there will be progress. This is a rapidly growing

field, with research funds provided by large medical device manufacturers and even the government. We will be able to help a large population with neurological or neuromuscular diseases.

7.1 Future Work

The demonstration of Section 6.2 represents a basic idea of what a mind-controlled could be in the future. If a simple 3-state mind-controlled prosthesis was built with “playable” devices such as the MindWave Mobile and the Mindstorms NXT, it can be said that using more sophisticated technology, imagination has no limits.

For example, using these 3-states, other patterns could be recognized. Infinite combinations of the states could be send to the prosthesis, each one meaning a different action. For instance, blink-blink in less than a 10 seconds interval could mean to move the arm to the left and then to the right. Or up and then down. Or blink-focus in the same period could mean move move the arm up and move the hand as saying hi. Or 4 blinks could mean close hand as a punch.

The ideal future work for this thesis would be to use this model in a more sophisticated robotic arm that could take more states. With more sophisticated programming languages such as C or Python, other movements could be shown. A regular EEG device (20 electrodes) could be used to get more signal quality. Even a surface EMG would be set in the forearm to check if the movements correspond to their signal (and improve the EMG generator from Chapter 5). The brainwave-to-EMG coding is another main issue to be solved in the future.

The future in clinical applications is key. Paralyzed or amputees could see their dreams come true with the aid of prosthesis. A 26-joints robotic arm that can curl up to 45 pounds and is controlled with the mind was built last May [61]. Last August, an exoskeleton has been controlled just with human thought [62]. This is an example about the next-gen prosthetics: noninvasive and wireless brain-controlled devices.

Not just prostheses, any kind of robotics could be controlled with the mind. The bed of a paralyzed patient could be adjusted by him sending brain instructions. Or he could control

the TV and change the station, or turn the lights on or off [63]. Again, the possibilities are limitless.

We understand that future work on brainwave to EMG commands is an important aspect that can be now taken by researchers who read this thesis.

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APPENDIX A

Physical interpretation of the Hodgkin and Huxley model

A.1 Circuit equivalent

A typical circuit for a plasma membrane is shown in Fig. A.1, developed by Finkelstein and Mauro.

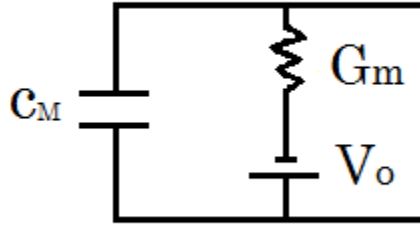


Figure A.1: The Finkelstein-Mauro model circuit equivalent of a plasma membrane

To calculate V_o and G_m , we are going to take into account anion and cation concentrations (ρ_A and ρ_C , respectively):

$$\begin{aligned} J &= (\sigma_A + \sigma_C)E + q\mu D \frac{\partial}{\partial x}(\rho_A - \rho_C) = \\ &= q\mu E(\rho_A + \rho_C) + q\mu D \frac{\partial}{\partial x}(\rho_A - \rho_C). \end{aligned} \tag{A.1}$$

Now we divide all terms by $\rho_A + \rho_C$ and integrate from one surface of the membrane to the other to obtain the voltage in the membrane

$$\frac{J}{\rho_A + \rho_C} = -q\mu \frac{\partial V}{\partial x} + \frac{q\mu D}{\rho_A + \rho_C} \frac{\partial}{\partial x}(\rho_A - \rho_C) \quad (\text{A.2})$$

$$V_M = \int_0^w \frac{\partial V}{\partial x} dx = -\frac{J}{q\mu} \int_0^w \frac{dx}{\rho_A + \rho_C} + D \int_0^w \frac{d(\rho_A - \rho_C)}{\rho_A + \rho_C}. \quad (\text{A.3})$$

The first term in (A.3) is due to a current passing through a resistance ($J = \sigma E$) and the second term is an offset potential. Finkelstein and Mauro defined this as

$$G_m = \frac{q^2}{\int_0^w \frac{dx}{\rho_A + \rho_C}} \quad (\text{A.4})$$

$$V_o = \frac{D}{\mu} \int_0^w \frac{d(\rho_A - \rho_C)}{\rho_A + \rho_C}. \quad (\text{A.5})$$

So Eq. (A.3) can be rearranged as

$$V_M = -\frac{Jq}{\mu G_m} + V_o \quad (\text{A.6})$$

$$J = (V_o - V_M) \frac{\mu G_m}{q} \quad (\text{A.7})$$

$$\frac{\partial J}{\partial x} = \frac{\partial}{\partial x} \left((V_o - V_M) \frac{\mu G_m}{q} \right) = -\frac{\partial \rho}{\partial t}. \quad (\text{A.8})$$

A.2 Physical interpretation of the Hodgkin-Huxley model with a linear capacitance

The first equation of the Hodgkin and Huxley model comes as follows

$$I_m = C_m \frac{dV}{dt} + [G_m(V - V_K) + G_{Na}(V - V_{Na}) + G_L(V - V_L)], \quad (\text{A.9})$$

which we could define as

$$I_m = I_{\text{cap}} + I_{\text{ohm}} \quad (\text{A.10})$$

or

$$J_m = J_{\text{cap}} + J_{\text{ohm}}, \quad (\text{A.11})$$

where

$$J_{\text{ohm}} = J_{\text{drift}} + J_{\text{diffusion}} = \sigma E - qD \frac{\partial \rho}{\partial x}, \quad (\text{A.12})$$

and J_{cap} comes from

$$\begin{aligned} \bar{\nabla} \cdot \bar{D} &= \rho \\ \iiint (\bar{\nabla} \cdot \bar{D}) dV &= \iiint \rho dV = Q \\ \iint \bar{D} d\bar{A} &= Q. \end{aligned} \quad (\text{A.13})$$

For a linear capacitance, constant $D = \epsilon E$,

$$\begin{aligned} Q &= DA \\ \frac{dQ}{dt} &= A\epsilon \frac{dE}{dt} \\ J_{\text{cap}} &= AC \frac{dV}{dt}. \end{aligned} \quad (\text{A.14})$$

So, to put the first HH equation in a one-dimension continuity equation format

$$\frac{\partial}{\partial x} J_m = \frac{\partial}{\partial x} \left(\sigma E - qD \frac{\partial \rho}{\partial x} + AC \frac{dV}{dt} \right) = -\frac{\partial \rho}{\partial t}. \quad (\text{A.15})$$

A.3 Physical interpretation of the Hodgkin-Huxley model with a nonlinear capacitance

A new interesting case we would have to consider is, if C or D depend on the concentration $(C(\rho), D(\rho))$,

$$Q = C(\rho)V \rightarrow \frac{dQ}{dt} = C(\rho)\frac{\partial V}{\partial t} + V\frac{\partial C(\rho)}{\partial t}, \quad (\text{A.16})$$

the first HH would be

$$J_m = \sigma E - qD(\rho)\frac{\partial \rho}{\partial x} + C(\rho)\frac{\partial V}{\partial t} + V\frac{\partial C(\rho)}{\partial t}. \quad (\text{A.17})$$

As a one-dimension continuity equation format:

$$\frac{\partial}{\partial x} J_m = -\sigma \frac{\partial^2 V}{\partial x^2} - q \frac{\partial}{\partial x} D(\rho) \frac{\partial \rho}{\partial x} - D(\rho) \frac{\partial^2 \rho}{\partial x^2} + C(\rho) \frac{\partial}{\partial x} \left(\frac{\partial V}{\partial t} \right) + V \frac{\partial}{\partial x} \left(\frac{\partial C(\rho)}{\partial t} \right) = -\frac{\partial \rho}{\partial t}. \quad (\text{A.18})$$